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ORIGINAL ARTICLES

PROLONGED OBSTRUCTIVE JAUNDICE IN INFANCY

1. General Survey of 156 Cases

By DAVID YI-YUNG HSIA, M.D., PAUL PATTERSON, M.D., FRED H. ALLEN, JR., M.D., LOUIS K. DIAMOND, M.D., AND SYDNEY S. GELLIS, M.D.

Boston

PROLONGED obstructive jaundice in infancy continues to be one of the most difficult problems in clinical pediatrics. There is confusion as to the exact etiology of the jaundice, uncertainty as to the selection of cases which should be explored surgically, and meager data with regard to the ultimate course of the patients who are treated either medically or surgically.

In 1916, Holmes[1] first defined the signs and symptoms of congenital atresia of the bile ducts and called attention to the fact that some of the infants might be cured if surgical procedures could accomplish anastomosis of the biliary tract above the point of obstruction to the alimentary canal. In 1927, Ladd[2] performed the first successful operation for the relief of congenital atresia of the bile ducts and the subsequent work on five other cases has been reported by his group.[3-5] Gray[6] reviewed the world literature and found that only 15 cases of congenital biliary atresia had been successfully treated with anastomosis; since then Rosemond[7] has reported on one additional case.

The other causes of prolonged obstructive jaundice have received much speculation. Ladd[3] mentioned that some of the cases of obstructive jaundice were due to "inspissated bile" with stenosis or narrowing of the common duct causing partial obstruction to the bile flow, but with no definite evidence of atresia. This concept has subsequently been mentioned by various authors, but no large series of cases has been analyzed or reported.

From the Medical Service and Blood Grouping Laboratory of the Children's Medical Center, the Department of Pediatrics of the Beth Israel Hospital, and the Department of Pediatrics, Harvard Medical School, Boston.

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Stokes et al.[8] have recently reported viral hepatitis in the newborn infant as a cause of jaundice in infancy and has stated that this condition must be considered in the differential diagnosis of obstructive jaundice. Patterson[9] has reported on the successful use of cholegogues in the treatment of infants with obstruction jaundice due to "bilary insufficiency." Gerrish and Cole[10] have reported a study of jaundice in infants and children under 12 years of age and classified them according to "medical" and "surgical" jaundice. However, most of their patients appear to be in the older age group.

In order to obtain a better understanding of obstructive jaundice in infancy, an analysis was made of 156 infants admitted to the Children's Medical Center in Boston with the clinical picture of prolonged obstructive jaundice. Follow-up data on the ultimate course has been obtained in 85% of the cases analyzed.

Methods and Materials

All the infants between the ages of 3 wk. and 1 yr. of age who had prolonged obstructive jaundice admitted to the Children's Medical Center between 1940 and 1951 were included in this study. All patients who showed definite evidence of nonobstructive jaundice such as sepsis, congenital and acquired hemolytic anemia, sickle cell anemia, etc., were excluded. Erythroblastosis fetalis patients who followed a normal course of recovery were excluded from the series, but those who developed the "inspissated bile" syndrome were included. The 2 groups can be readily differentiated as will be shown later. The series as a whole included all patients who were thought to have prolonged jaundice due to some type of obstruction and most of the cases were admitted to the hospital with a tentative diagnosis of biliary atresia with a view to possible surgery.

All the patients had a routine history and physical examination with careful notation of data regarding onset of jaundice, color of stools and urine, and size of liver and spleen. All had blood counts, urinalysis, serologic tests for syphilis, and urine and stool studies for bile and urobilinogen. Also, liver function tests were performed for all of them. Prior to 1947, only the limited tests then available were used, but since that time, all have had complete liver function studies which include cephalin-cholesterol flocculation, thymol turbidity, thymol flocculation, and 1 min. and 30 min. serum bilirubin levels. Also, since 1947, most of the patients and their parents have had blood grouping studies in order to demonstrate possible blood incompatibilities. The majority have had duodenal intubation to determine presence of bile and tryptic activity; and in the last 2 yr., many have been treated with decholin® and ketachol® in an attempt to promote secretion of bile.[9] Liver biopsies were obtained in about half of the patients explored surgically. This paper consists of clinical descriptions; detailed data on use of liver function tests, blood grouping tests in differential diagnosis, and use of cholegogues in the treatment of those conditions will be reported later.

Results are shown in table 1. The cases fall into four categories: (1) true biliary atresia, (2) inspissated bile due to erythroblastosis fetalis, (3) inspissated bile of unknown etiology and (4) other causes. These will be analyzed separately, and representative case histories will be presented.

I. Biliary Atresia

Ninety-four of the 156 patients had biliary atresia proved by surgical exploration. This group represents 60% of the entire series of patients.

Follow-up studies were successfully obtained in 67 of the 94 cases or 72% of the patients with proved biliary atresia. Of these, 55 are known to be dead, 6 in whom anastomosis could not be performed are terminally ill with jaundice and cirrhosis and are considered therapeutic failures, 4 were successfully treated by anastomosis and are now doing well, and 2 showed clearing of jaundice and are now well despite apparent inoperability at the time of exploration. Follow-up studies could not be obtained as to 16 who were operated on 4 or more years previously, and 11 were explored too recently

TABLE 1

156 CASES OF PROLONGED OBSTRUCTIVE JAUNDICE IN INFANCY

I. BILIARY ATRESIA				94 (60%)
A. Follow-up Complete				
1. Dead			55	
2. Terminally ill with cirrhosis			6	
3. Successfully anastomosed			4	
4. Well despite no anastomosis			2	
B. Follow-up Incomplete				
1. Exploration too recent to evaluate			11	
2. No Follow-up			16	
II. INSPISSATED BILE DUE TO ERYTHROBLASTOSIS (All living and well at present)				23 (15%)
III. INSPISSATED BILE OF UNKNOWN ETIOLOGY				30 (19%)
A. Follow-up Complete				
1. Dead			6	
due to cirrhosis		2		
due to cholangitis		2		
due to unrelated cause		2		
2. Cirrhotic			2	
3. Living and well			18	
B. No Follow-up			4	
IV. OTHER CAUSES				9 (6%)
1. Hepatitis	(1 dead)		4	
2. Hemangioendothelioma	(dead)		1	
3. Node compression	(dead)		1	
4. Portal vein thrombosis	(dead)		1	
5. Niemann-Pick's disease			1	
6. Unknown cause			1	

to be evaluated properly. Complete details on this group will be given in a paper from the Surgical Service of the Children's Medical Center.

II. INSPISSATED BILE DUE TO ERYTHROBLASTOSIS FETALIS

After excluding all cases of true biliary atresia, there is left a large group which shows obstructive jaundice without atresia. A few of these are due to specific causes such as infectious hepatitis, and hemangioendothelioma which will be discussed under a later section. However, most of them fall into the classification of nonspecific obstructive jaundice or "inspissated bile" as defined by Ladd. Although it is certain that not all the cases in this group belong to the physiologic and pathologic entity of "inspissated bile," the term is a descriptive and useful one since there is at present no more specific term for the condition.

In analyzing the cases having inspissated bile, it was found that almost half had the condition as a result of a specific etiology, namely, erythroblastosis fetalis. The authors believe this represents a relatively new clinical entity and should be considered as a major cause of obstructive jaundice in infancy. The diagnosis may be made on the basis of the following criteria: (1) Jaundice appears in the first two days of life and in most cases in the first few hours of life. (2) The jaundice is persistent and lasts for more than the first three weeks of life. (3) The patient demonstrates an obstructive type of jaundice as shown by the marked elevation of both direct and indirect bilirubin levels. (4) All the

flocculation tests are negative. (5) Blood grouping studies show a definite blood incompatibility between the mother and child and there is evidence of erythroblastosis in the child.

The syndrome of inspissated bile due to erythroblastosis fetalis can be differentiated from the usual course of erythroblastosis fetalis by the persistence of clinical jaundice and the elevation of both the one minute and total serum bilirubin for weeks after birth. In the usual patient with erythroblastosis fetalis who is treated with exchange transfusions, jaundice seldom persists after 7 days and never after 10 days. Even in untreated patients or those given small transfusions jaundice disappears by three weeks in most case. In inspissated bile due to erythroblastosis, the jaundice persists for 3 to 15 weeks and the clinical course differs in no way from that seen in biliary atresia or inspissated bile of

TABLE 2

BILIRUBIN LEVELS IN PATIENTS WITH ERYTHROBLASTOSIS WITH AND WITHOUT INSPISSATED BILE SYNDROME

	Erythroblastosis without Inspissated Bile		Erythroblastosis with Inspissated Bile	
Day	1 min.	Total	1 min.	Total
Cord	0.13 mg./100 cc.	3.74 mg./100 cc.	0.32 mg./100 cc.	3.12 mg./100 cc.
1	0.45 "	31.80 "	0.71 "	24.9 "
2	0.52 "	16.60 "	1.25 "	18.9 "
3	0.45 "	15.56 "	4.00 "	27.0 "
4	0.65 "	13.5 "	10.00 "	25.6 "
5	0.38 "	7.94 "	24.3 "	48.0 "
6	0.23 "	4.88 "	21.3 "	43.5 "
21			1.23 "	3.24 "

unknown etiology. The infant with erythroblastosis fetalis without obstruction shows a marked elevation of the indirect bilirubin fraction, but the direct fraction stays normal throughout, whereas in the patient with inspissated bile due to erythroblastosis, there is a progressive elevation of direct as well as indirect bilirubin. This is illustrated in table 2 in which a patient with inspissated bile and erythroblastosis is compared with a patient with erythroblastosis who had no obstruction.

Altogether 23 cases of inspissated bile due to erythroblastosis fetalis were found in the present study which represents 15% of the total group. All the 23 patients showed blood incompatibilities and the infants had laboratory confirmation of erythroblastosis fetalis. Twenty-one of the cases were due to Rh, 1 due to Hr and 1 due to ABO incompatibility. Twenty-one of the 23 patients had onset of marked jaundice within the first day of life and in most instances in the first hour of life. The remaining two patients were reported to have become jaundiced on the second day of life, but it is possible that jaundice may have been present and missed by the observers. The jaundice lasted from a minimum of 3 weeks to a maximum of 5½ months with most of the cases seen in the range of 7 to 8 weeks. All the patients demonstrated markedly elevated direct and total serum bilirubin as determined between 6 days to 14 weeks of life. The most severely jaundiced patient had a one minute bilirubin of 38.6 and a total serum bilirubin of 69.8 mg./100 cc. The least severely jaundiced patient had a one minute bilirubin of 1.8 and a total serum bilirubin of 4.08 mg./100 cc. All had negative flocculation tests.

Ten of these 23 patients were admitted with a diagnosis of biliary atresia for surgery and a history of erythroblastosis fetalis was unknown prior to study. In the remaining 13, the presence of erythroblastosis was known, but the patients were referred because of prolonged jaundice. It is interesting to note that of the 23 patients, only two were considered to have had adequate therapy.[11] Of the others, 17 had received either no treatment or multiple small transfusions, 3 had received one exchange transfusion only, and 1 had had a repeat exchange transfusion, the first one having been given after the baby was 24 hours old. All 23 of the patients are now alive and well, free of jaundice, passing normal-colored stools, and are apparently free from liver disease.

Whether inspissation occurs as a result of damage to the liver parenchyma by erythroblastosis as suggested by Craig[12] or whether the excessive load of bilirubin presented to the liver causes blocking of the ducts during the process of excretion is not clear. In the former case, it is possible that excessive hematopoesis plus the presence of massive amounts of pigment in the liver results in poor production of biliary secretions and that it is the biliary "insufficiency" in the first few days of life that leads to a state of stasis, inspissation and obstruction. In the later case, the hemolytic process of erythroblastosis may produce an overload of pigment causing stasis and finally complete block. As the hemolytic process ceases, and the bile ducts become larger, the inspissation gradually clears and the bile passes normally, apparently leaving no sequelae. The fact that it occurs in some patients and not in others may be due to the differences of severity of the hemolytic process resulting in different pigment loads for the bile ducts and may also be due to the variation in functional maturity of the liver and size of bile ducts in infants. The fact that the condition is seen less frequently in infants treated by exchange transfusions suggests that the former theory may be more likely since by such exchange the infant's sensitized cells and indirect bilirubin are removed whereas the liver parenchyma is probably unaffected by the exchange transfusions.

The following case history is typical:

B. D., a white male infant, was first seen at Children's Medical Center at 7 wk. of age because of persistent jaundice. History revealed that mother had received 4 transfusions of Rh-positive blood after previous pregnancy because of postpartum hemorrhage. Infant was jaundiced at birth and became severely so at end of 24 hr. He was also noted to be severely anemic on 5th hospital day and was given small transfusions. At this time, patient was noted to be spastic and assumed a position of opisthotonus. Jaundice persisted, urine remained dark and stools were acholic. Laboratory studies at other hospital showed a direct bilirubin of 26 mg./100 cc. and a total bilirubin of 46 mg./100 cc. Physical examination on admission showed a spastic jaundiced infant. Liver was 3 cm. and spleen 1 cm. below costal margin. There were prominent veins over the abdominal wall. Laboratory studies showed bile in urine and urobilinogen in stools. Duodenal intubation revealed greenish material unaffected by decholin® and magnesium sulfate. Thymol turbidity was 1.2, thymol flocculation 0, cephalin-cholesterol flocculation 0, 1 min. serum bilirubin 9.06 and total serum bilirubin 18.8 mg./100 cc. Father's blood group was $O_{++\infty}$, the mother was $O_{\infty\infty+}$, with an anti-D titer of 1:4096 and anti-C titer of 1:64. Infant was $O_{++\infty}$. Coomb's ++++ with an anti-D titer in albumin of 1:64.

Patient was diagnosed as having erythroblastosis with kernicterus. Jaundice was thought to be due to inspissated bile from erythroblastosis and the patient was therefore not explored. One month later, thymol turbidity was 1.0, thymol flocculation 0, cephalin-cholesterol flocculation 0, 1 min. serum bilirubin 4.6 and total serum bilirubin 8.7 mg./100 cc. Two years later, when next seen, the infant was completely free of jaundice, was passing normal stools, but was mentally retarded and spastic.

This patient was the only one in the series who developed kernicterus, but the remainder of the clinical course was typical of the entire group.

III. Inspissated Bile of Unknown Etiology

After eliminating cases with inspissated bile that appeared to be definitely due to erythroblastosis, there are left those in which no specific etiology was found. Blood-grouping studies have been obtained in half of these cases and no blood incompatibilities could be demonstrated. Blood-grouping studies were not obtained in the other half, but the clinical picture in most did not resemble that of erythroblastosis and the number having true erythroblastosis fetalis which may have been overlooked in this group of patients is probably small.

The syndrome of inspissated bile of unknown etiology includes a total of 30 cases and represents 19% of the entire series. Follow-up studies have been successfully obtained in 26 of the 30 and therefore are 86% complete. Of these 26 with satisfactory follow-up data, 6 are known to be dead. Of these, 2 died of cholangitis postoperatively, 2 died of cirrhosis and 2 died of totally unrelated causes. One of these died of encephalitis several years after the jaundice disappeared and the other died of polycystic disease of the kidney in infancy. Two are alive but have definite cirrhosis and 18 are living and well with no jaundice. Follow-up data could not be obtained on 4.

Surgical exploration was undertaken in 20 of the 30 patients. All of these were found to have intact extrahepatic ducts, but in 4 these were thought to be small and stenotic although not atretic. Of the 20 that were explored, 12 were found to have bile of normal consistency, 5 were found to have bile which appeared thicker than usual, 1 was found to have dried-up stringy mucus which may have contained bile, and no mention of the aspirated contents was made in the other 2 cases. In all instances saline or methylene blue was injected into the gall bladder and found to pass freely into the duodenum.

Ten patients were not explored and were either not treated or were given decholin® and ketachol®. It is important to note that all but two of the patients who died or developed cirrhosis were among those explored.

It appears from the above data that 60% or more of the patients in this group will recover without sequelae. A small percentage of the patients will develop cirrhosis despite treatment and another small group of the patients will die as a result of either cirrhosis or the complications of surgery. Although the number of cases analyzed is small, there is some suggestion that surgical exploration should be avoided if possible.

The pathogenesis of this condition is still poorly understood. Detailed analyses showed that parity, course of pregnancy, and delivery were essentially normal in all 30 cases. Although a history of intermittent jaundice in a distant relative was obtained in 2, they were not studied by the authors and familial nonhemolytic icterus could not definitely be excluded. Nine were premature by weight and duration of gestation and several others had low birth weights. Jaundice appeared within 48 hours after birth in only 6 instances. In 2, there was a clinical picture consistent with erythroblastosis although blood grouping tests were not available to confirm the diagnosis. There was a history of severe illness in the first few days in 4 infants; 2 of these had vomiting with dehydration, 1 had pyloric stenosis, and the other had polycystic disease of the kidneys. Although no instance of true intrahepatic biliary atresia as described by Ahrens et al.[13] was seen, 1 infant showed immature transitional cells in place of the bile ducts.

On the basis of the available data, it would appear that the inspissated bile syndrome may occur as a result of different etiologies. Small bile ducts, hepatic immaturity, and dehydration may play a role in causing biliary stasis and inspissation. Early congenital cirrhosis of the liver with jaundice, infectious hepatitis and cholangitis cannot be definitely ruled out in all cases.

The following case history represents one of the patients who was treated adequately and developed cirrhosis in spite of treatment:

K. P., a white female infant, was first seen at Children's Medical Center at 4 wk. of age with complaint of jaundice since age of 3 days. This had subsequently become more marked. Urine also became dark and stools quite pale. Physical examination on admission showed a jaundiced infant whose liver was 3 to 4 cm. below costal margin. Laboratory studies showed bile but no urobilinogen in urine and stools negative for bile. Liver function tests showed a thymol turbidity of 0.2, thymol flocculation 0, colloidal red 0, cephalin-cholesterol flocculation plus-minus, 1 min. serum bilirubin 4.3, and total serum bilirubin 7.25 mg./100 cc. Blood grouping studies showed the father to be $B_{++++}{}^{++++}{}_{0}{}^{++++}$, the mother to be $A_{++++}{}^{++++}{}_{0}{}^{++++}$ with a negative titer. Infant was $A_{\infty 0}{}^{++++}$ and a negative titer and a negative Coomb's test. Mother's and child's cells did not agglutinate. Because of above data, patient was explored on 13th hospital day and bile ducts were found to be patent throughout.

Postoperatively, a small amount of bile was found in stool. Duodenal intubation, however, showed only scant flow and absence of bile. Liver function tests revealed a thymol turbidity of 1.0, thymol flocculation 0, cephalin-cholesterol flocculation 0, 1 min. serum bilirubin 2.99 and total serum bilirubin 5.20 mg./100 cc. At 9 mo. of age, patient was still icteric and showed early signs of cirrhosis. At age of 1 yr., he developed frequent nosebleeds and was treated with methionine® and decholin®. After treatment, liver function tests showed a thymol turbidity, a thymol flocculation 0, cephalin-cholesterol flocculation 0, 1 min. serum bilirubin 0.64, and total serum bilirubin 1.31 mg./100 cc. However, patient continued to show cirrhosis of liver with liver 7 cm. and spleen 6 cm. below costal margin. There were esophageal varices by roentgenographic examination and continued epistaxis. When last seen at 1½ yr. of age, patient had a large distended abdomen with engorged veins, was slightly icteric, and had frequent epistases. Liver function tests showed a thymol turbidity of 0.5, thymol flocculation 0, cephalin-cholesterol flocculation 0, 1 min. serum bilirubin 1.10 and total serum bilirubin in 2.33 mg./100 cc.

This patient shows that despite patency of the ducts, the obstructive phenomena had caused irreversible changes to the liver parenchyma. It is possible that this infant had congenital cirrhosis; clinically, however, it differed in no way from the infants who recovered. The exact relationship of so-called congenital cirrhosis to this syndrome remains to be determined.

The following case illustrates a patient who was successfully treated without surgical exploration:

P. K., a white male infant, was first seen at Children's Medical Center at 4 wk. of age because of prolonged jaundice. Jaundice was first noted at birth and had subsequently increased and persisted. Stools were light and urine dark. Physical examination on admission showed an icteric infant with liver 4 cm. and spleen 1½ cm. below costal margin. Laboratory studies showed bile in urine and urobilinogen was present at 1:4 dilution. Stools varied from a faint trace to a trace of bile. Duodenal intubation showed fluid to be viscid but contained no bile. Liver function tests showed a thymol turbidity of 0.8, thymol flocculation 0, cephalin-cholesterol flocculation 0, 1 min. serum bilirubin 3.09, and total serum bilirubin 5.4 mg./100 cc. Alkaline phosphatase was 16.6 Bodansky units with a phosphorus of 7.6. Prothrombin time was 12.7 with a control of 13.4 sec. Blood-grouping studies showed the father was A_{++0+}, the mother was AB_{++0+}. Infant was A_{++0+} with a negative Coomb's. Father's and mother's cells did not agglutinate.

Patient was treated with ketachol® with some apparent improvement in hospital. Liver function tests showed a thymol turbidity of 0.2, thymol flocculation 0, cephalin-cholesterol flocculation 0, 1 min. serum bilirubin 1.85, and total serum bilirubin 3.16 mg./100 cc. When last seen at 8 mo. of age, patient was doing well, was completely free of jaundice, and was passing normal-colored stools. He had some intolerance to fat, but was otherwise gaining and developing normally.

IV. Other Causes

Nine patients had conditions other than that due to either biliary atresia or inspissated bile. Four had infectious hepatitis, of whom 1 died and the other 3 are living and presumed to be well. One patient had a hemangioendothelioma, was explored, and died 8 hours

postoperatively. One patient had a lymph node pressing on the bile ducts and although successfully relieved surgically, the infant died of high intestinal obstruction due to adhesions one month later. One patient entered the hospital with cirrhosis and ascites at the age of 1½ months and died despite repeat paracentesis, human albumin therapy, etc. At autopsy, the patient was found to have a questionable portal vein thrombosis which was thought to be secondary to an umbilical infection early in life. One patient had Niemann-Pick disease proved by bone marrow and lymph node biopsy and was thought to have obstructive jaundice on the basis of enlarged nodes. She was not explored. One patient had a persistent jaundice for which no specific etiology could be found. This cleared spontaneously at about 4 months of age and the child has remained well since then. He was not considered to have inspissated bile because he passed bile in the stools and uroblinogen in the urine consistently. He may have had infectious hepatitis but this was never proved.

The four cases classified as infectious hepatitis were diagnosed in three instances by liver biopsies and in the fourth case the diagnosis was suggested by the markedly positive flocculation tests. Unfortunately, passage of virus was not undertaken in any of the patients.

The following case history is representative:

R. T., a white male infant, was first seen at Children's Medical Center at 7 wk. of age because of persistent jaundice. Child was noted to have yellow sclerae on 10th day of life and had clay-colored stools from that time. Physical examination on admission showed an infant who was moderately jaundiced with a distended abdomen and a liver 2½ cm. below costal margin. Spleen could not be felt. Thymol turbidity was 4.5, thymol flocculation plus-minus, cephalin-cholesterol flocculation 2+, 1 min. serum bilirubin 9.2, and total serum bilirubin 17.3 mg./100 cc. Duodenal intubation showed no bile but adequate trypsin. In view of fact that clinical and laboratory picture was consistent with that of biliary atresia, patient was explored and at surgery was found to have patency of all the ducts which were flushed with saline with ease. A biopsy of liver showed liver cells with great variation in size and shape. There was much bile and intense vacuolation within cells. Numerous cells in the parenchyma were necrosed and invaded by polymorphonuclear leukocytes. There was no proliferation of bile ducts and no collapse of the reticulum in most areas. There was no fibrosis.

Conclusions

One hundred fifty-six cases of prolonged obstructive jaundice seen at the Children's Medical Center between 1940 and 1951 have been investigated and in 85% of the patients follow-up studies have been carried out.

Ninety-four (61%) were due to true biliary atresia.

Twenty-three (15%) were due to inspissated bile associated with erythroblastosis. All these patients are living and well and free of jaundice. The diagnosis of this condition can be made when the patient has (1) jaundice during the first two days of life with persistence of jaundice for over three weeks, (2) a high direct and indirect bilirubin compatible with obstructive jaundice, (3) negative flocculation tests, (4) blood-grouping studies consistent with erythroblastosis.

Thirty (19%) were due to inspissated bile of unknown etiology. Of these 6 are dead, 2 are alive but cirrhotic, and 18 are living and well and no follow-up was obtained on the four other cases. There appears to be some relationship between this condition and immaturity of the liver, small extrahepatic ducts, thickened secretions, and possibly dehydration.

Nine (6%) were due to miscellaneous causes, of which four cases were probably due to infectious hepatitis.

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SPANISH ABSTRACT

Ictericia Obstructiva Prolongada en la Infancia
1. Análisis General de 156 Casos

La ictericia obstructiva prolongada de la infancia continúa siendo uno de los problemas mas difíciles en la clínica pediátrica pues existe confusión acerca de la etiología exacta de la ictericia, incertidumbre respecto a la selección de los casos que deben explorarse quirúrgicamente y datos escasos en relación a la evolución posterior de los enfermos que fueron tratados médica o quirúrgicamente.

Desde 1916 en que Holmes definió por primera vez los signos y síntomas de la atresia congénita de los conductos biliares y planteó las posibilidades quirúrgicas de tratamiento, hasta 1948 se han reportado 16 casos de atresia biliar congénita tratados con éxito por anastomosis. Ladd introdujo el concepto de ictericia obstructiva debida a "bilis espesa" con estenosis del colédoco produciendo una obstrucción parcial del flujo biliar pero sin evidencia franca de atresia, pero este cuadro no se ha estudiado más detenidamente. Ultimamente la posibilidad de hepatitis viral en el recién nacido ha sido demostrada por Stokes. Con objeto de entender mejor la ictericia obstructiva prolongada de la infancia los autores hicieron la revisión de 156 casos y reportan los datos de evolución en el 85% de los casos estudiados.

Los casos seleccionados fueron en general todos aquellos en que se pensó que tenían ictericia prolongada debida a algun tipo de obstrucción y que se hospitalizaron con diagnóstico posible de atresia biliar con la mira de alguna posibilidad quirúrgica. Se eliminaron aquellos que definitivamente tenían ictericia por sepsis, anemia hemolítca congénita o adquirida etc, y los de eritroblastosis fetalis que siguieron su curso normal hasta la curación pero incluyendo, de estos niños eritroblastósicos, los que desarrollaron el "síndrome de bilis espesa."

Los casos cayeron dentro de 4 grupos etiológicos: (1) Atresia biliar verdadera, (2) Bilis espesa debida a eritroblastosis fetalis, (3) Bilis espesa de etiología desconocida, y (4) Otras causas.

I.—Atresia Biliar.—Comprende el 60% de los enfermos o sean 94 enfermos y se comprobó por exploración quirúrgica. De este grupo han muerto 55 pacientes, 6 estan con cirrosis terminal, 4 fueron anastomosados con éxito y están bien, otros 2 están igualmente bien a pesar de que no se hizo anastomosis alguna aparentemente por ser inoperables al explorarse, 16 no se sabe su evolución y 11 han sido operados tan recientemente que no puede hacerse pronóstico de curación.

II.—Bilis espesa debida a eritroblastosis fetalis.—Excluyendo los casos de atresia biliar verdadera

queda un grupo de enfermos que en su gran mayoría caen dentro de la clasificación de ictericia obstructiva no específica o por "bilis espesa" y analizando estos casos se encuentra que casi la mitad tenían dicho proceso por eritroblastosis fetalis. Creen los autores que el cuadro representa una entidad clínica relativamente nueva y debe considerarse como una causa importante de ictericia obstructiva en la infancia. El criterio diagnóstico es el siguiente: (1) Ictericia que aparece en los primeros 2 días de la vida y en la mayoría de los casos en las primeras horas, (2) Ictericia persistente y presente durante más de las primeras tres semanas de la vida, (3) Ictericia de tipo obstructivo a juzgar por la elevación marcada tanto de la bilirrubina directa como de la indirecta, (4) Todas las pruebas de floculación son negativas y (5) Los estudios de grupo sanguíneo demuestran definitivamente incompatibilidad sanguínea entre la madre y el niño y es evidente el cuadro de eritroblastosis en el niño.

El síndrome de bilis espesa debida a eritroblastosis fetalis puede diferenciarse del curso usual de una eritroblastosis fetalis por la persistencia clínicamente de la ictericia pues en el síndrome varía entre 3 y 15 semanas y el curso clínico no difiere en forma alguna del de la atresia biliar o el de bilis espesa de causa desconocida. Cuando se trató de la ictericia de la eritroblastosis fetalis exclusivamente cuya terapéutica se hizo con exsanguinotransfusiones, raramente persiste después de 7 días y nunca después de 10, y aún en pacientes no tratados o tratados con pequeñas transfusiones desaparece en la mayor parte de los casos a las 3 semanas. Además, en el síndrome tanto la bilirrubina directa como la indirecta se elevan progresivamente mientras que en la eritroblastosis sin obstrucción biliar por bilis espesa, la bilirrubina indirecta está muy elevada y la directa permanece normal durante todo el tiempo.

Fueron 23 casos o sea el 15% del grupo total los que manifestaron el síndrome, 10 de estos se diagnosticaron al admitirse como atresias biliares y no existía historia de eritroblastosis fetalis, en los restantes, ésta era conocida pero por la ictericia prolongada solicitaron internamiento. Todo los pacientes viven, estan libres de ictericia y aparentemente sin lesión hepática.

La explicación del espesamiento de la bilis no es clara. Es posible que sea el resultado de la hematopoiesis excesiva mas la presencia en el hígado de cantidades masivas de pigmento que causan una producción escasa de secreciones biliares y que esta "insuficiencia biliar" de los primeros días de la vida lleve a un estado de estasis, espesamiento y obstrucción o bien que el proceso hemolítico de la eritroblastosis determine una sobrecarga de pigmento causando estasis y finalmente bloqueo completo y a medida que la hemólisis cesa, y los conductos biliares se hacen mas grandes, el espesamiento biliar cede gradualmente y la bilis drena normalmente, no dejando secuela alguna. Ambas posibilidades tienen hechos en pro y en contra.

III.—Bilis espesa de etiología desconocida.—El número de los casos que cayeron en esta categoría fué de 30 y representan el 19% del total, la mitad fueron investigados desde el punto de vista de incompatibilidades sanguíneas y no se encontraron, el resto se incluye aquí porque el cuadro clínico no semejó el de la eritroblastosis fetalis y es muy posible que si la hubo fué en muy escasos enfermos. En 20 de ellos se hizo exploración quirúrgica y todos tenían sus conductos extrahepáticos permeables pero en 4 se pensó que eran pequeños y estaban estenosados pero no atrésicos, en 12 se encontró bilis de consistencia normal, en 5 parecía ser mas espesa que lo usual y en 1 había moco seco hilante que quizás haya tenido bilis. Con excepción de 2 enfermos todos los que murieron o desarrollaron cirrosis fueron explorados quirúrgicamente y la muerte fué bien por cirrosis o por complicaciones operatorias lo cual sugiere que la exploración quirúrgica debe ser evitada si es posible, ya que el 60% de los enfermos recuperan sin secuela aparente. Por los datos de las historias, parece ser que el síndrome de bilis espesa puede tener distintas etiologías. Los conductos biliares pequeños, la inmadurez hepática y la deshidratación pueden jugar cierto papel en la estasis y espesamiento biliar pero no se pueden eliminar, definitivamente, en todos los casos, la cirrosis hepática congénita temprana con ictericia, la hepatitis infecciosa y la colangitis.

IV.—Otras causas.—Este grupo lo formaron 9 enfermos, o sea el 6% del total; en ninguno había atresia biliar o bilis espesa. Cuatro tenían hepatitis infecciosa, 3 fueron diagnosticados por biopsia de hígado y el otro es sugestivo porque tuvo pruebas de floculación intensamente positivas. De los 5 restantes uno tenía un hemangioendotelioma, otro tenía un ganglio linfático que comprimía los conductos biliares, otro más trombosis de la porta quizás, el penúltimo tenía enfermedad de Nieman-Pick y posiblemente obstrucción biliar por adenopatía compresiva y el último quizás haya sido hepatitis infecciosa, curó a los 4 meses y está bien.

300 Longwood Avenue

INTESTINAL OBSTRUCTION IN THE NEWBORN INFANT DUE TO AGENESIS OF THE MYENTERIC PLEXUS (Congenital Megacolon)

By WILLIS J. POTTS, M.D., JOSEPH D. BOGGS, M.D., AND HARVEY WHITE, M.D.
Chicago

IT REQUIRES fifty years to establish a truth in medical literature and fifty years to remove an error." This flexible adage seems altogether appropriate to the subject of congenital megacolon (Hirschsprung's disease). As long ago as 1901 Tittel[1] called attention to changes in the ganglion cells of the myenteric plexus of the colon in a case of congenital megacolon and postulated that such changes might interfere with normal peristalsis. From then until 1948 sporadic case reports and studies appeared, all calling attention to the absence, scantiness or degeneration of ganglia in the constricted portion of the colon and the presence of normal ganglia in the dilated segment. In 1948 Zuelzer and Wilson[2] reported 11 cases of functional intestinal obstruction in the newborn infant due to congenital absence of nerve ganglia in the colon and concluded, "Further experience will be necessary to decide whether resection of part or of all of the non-motile portion of the intestine is a desirable and practical procedure."

Whitehouse and Kernohan[3] published a careful chronologic analysis of pertinent literature on the subject of congenital megacolon and from a detailed pathologic study of 11 such cases presented incontrovertible evidence that the pathogenesis of this disease lies in changes in the myenteric plexus. The gathered knowledge of almost 50 years culminated in the reasonable and logical surgical treatment as presented by Swenson and Bill[4] and of Swenson, Newhauser and Pickett.[5]

At present it is generally agreed that the proper treatment of congenital megacolon consists of removing the segment of bowel devoid of ganglia cells and re-establishing intestinal continuity by the so-called "pull-through" operation perfected by Swenson and his associates. The present authors routinely employ this method of surgical treatment in children with congenital megacolon.

This article is a report of 10 infants who were admitted to this hospital with symptoms of acute intestinal obstruction, but who were proved to have functional obstruction due to agenesis of the myenteric plexus of various portions of the colon.

SYMPTOMS AND DIAGNOSIS

Vomiting, constipation and abdominal distention during the first few days of life were the presenting symptoms in all cases. Often by the second day of life the infant began to vomit bile-stained material. Constipation in some infants was complete and on digital examination the rectum was empty. Others passed small amounts of meconium which was apt to be somewhat dry and sticky. The normal infant moves its bowels the first day of life. Digital examination occasionally was followed by a gush of normal meconium.

From the Departments of Surgery, Pathology and Roentgenology of the Children's Memorial Hospital and from the Otho S. A. Sprague Memorial Institute Laboratories, Chicago.

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In fact, one infant 2 days of age who had had no bowel evacuation and whose rectum was completely empty passed a large amount of meconium and air after a vigorous rectal examination. The infant's bowels continued to move spontaneously for one week. Vomiting stopped, feedings were taken well and the child was sent home. It was returned five days later dangerously ill with recurrent obstipation, vomiting and advanced dehydration.

Distention appears early as it does in cases of atresia of the bowel or rectum. Intestinal patterning is often visible. The examiner may be led astray because the symptoms vary so greatly in severity. One infant had obstipation, vomiting and distention for two days after birth, then proceeded to have normal bowel movements with the aid of suppositories and enemas for a few weeks. During this time vomiting was sporadic but not sufficiently severe to prevent a weight gain of 0.9 kg. More or less suddenly all bowel movements ceased, vomiting and distention recurred and the infant was readmitted to the hospital in a desperate condition.

If the symptoms are mild, of course, there may be no reason to suspect that the infant has anything more than mild constipation. Such cases are undoubtedly those which in later years become the typical cases of congenital megacolon.

Zuelzer found a definite familial tendency as evidenced by five cases in a family of 12 children. Forshall et al.[6] likewise found a familial tendency. Burnard[7] in a report of 23 cases found no familial tendency towards this disease. With one possible exception no familial tendency was noted in the cases reported here. One mother reported that a previous child had died of "twisted bowels" shortly after birth.

The diagnosis most commonly made by the present investigators until experience taught better was intestinal obstruction due to atresia of the bowel. Careful study of the roentgenograms and critical analysis of all findings usually makes it possible to differentiate the two conditions. Shiny green-black meconium in the rectum, even small amounts, is strongly indicative that the bowel is patent. Repeated digital examinations are helpful. If the parent, nurse or attendant gives a reliable report that the infant has passed a meconium stool, a diagnosis of atresia of the bowel is probably not in order. It is important, even though at times it may be impossible to make an absolute diagnosis, to bear in mind the possibility of neurogenic obstruction in order that proper surgical treatment may be planned.

Roentgenographic Studies

If intestinal obstruction in the newborn infant is suspected of being due to agenesis of the myenteric plexus RGs should always be made in the upright and the supine position. The upright film will demonstrate fluid levels and the supine film will assist in locating more definitely the point of bowel obstruction. In the case of a five day old child (Fig. 1A) with obvious intestinal obstruction RGs show multiple fluid levels some of which appear to be in the large bowel. In the supine views (Fig. 1B), however, it is obvious that there is gas both in the descending colon and in the rectosigmoid. In case of doubt a small barium enema, as suggested by Neuhauser, will be decisive not only in determining the location of the gas but also the point of transition between normal appearing and dilated bowel (Fig. 2). Although the junction between normal and dilated bowel is usually the point of change from normal to abnormal innervation, one cannot accept either the roentgenographic findings or the operative findings as infallible evidence of this junction. At times a considerable segment of dilated bowel contains no ganglia.

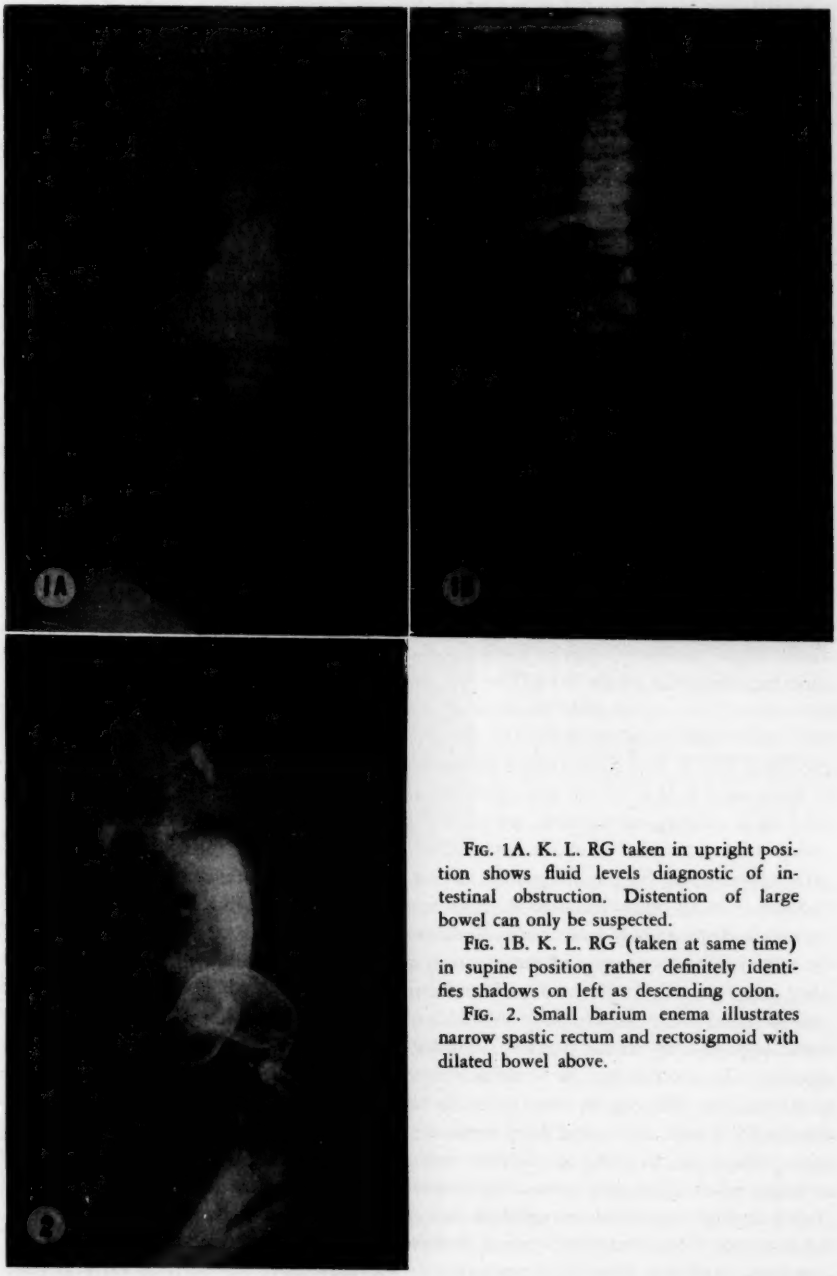


FIG. 1A. K. L. RG taken in upright position shows fluid levels diagnostic of intestinal obstruction. Distention of large bowel can only be suspected.

FIG. 1B. K. L. RG (taken at same time) in supine position rather definitely identifies shadows on left as descending colon.

FIG. 2. Small barium enema illustrates narrow spastic rectum and rectosigmoid with dilated bowel above.

In seven cases in which complete roentgenographic studies were made all had fluid levels diagnostic of bowel obstruction. Gas in the large as well as in the small bowel was definite in three cases and questionable in two. In two patients gas and fluid levels could be demonstrated only in the small bowel. However, one of these infants had fibrocystic disease of the pancreas as well as agenesis of the myenteric plexus.

Careful study of RGs taken in both the upright and the supine position will be an aid in the preoperative differentiation of atresia of the bowel from neurogenic obstruction.

Pathology

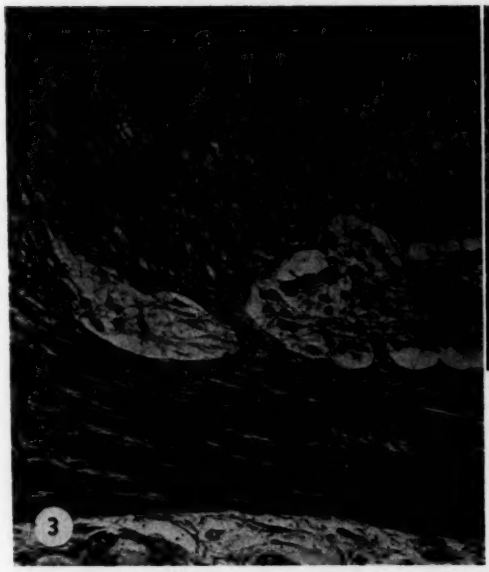
Auerbach's myenteric plexus may be defined as a continuous plexus of nerve cells beginning at the junction of the upper and middle third of the esophagus and extending to the anus. These nerve cells supply the inner circular and outer longitudinal muscle bundles and lie between these two bundles. Meissner's plexus lies within the submucosa. Here the nerve cells are smaller and less frequent than in Auerbach's ganglia. Irwin,[8] in a detailed and painstaking study of the anatomy of Auerbch's plexus in the guinea pig, was unable to demonstrate any communication between Auerbach's and Meissner's plexuses. In counting the number of myenteric ganglion cells in the colon and rectum of the guinea pig, he found a range of from 15,000 to 19,000 cells/sq. cm. It was noted that the ganglia differ in shape and arrangement.

That congenital megacolon is intimately related in an absence or marked diminution of ganglion cells has long been known. As early as 13 years after Hirschsprung's early communication, Tittel noted these changes. Robertson and Kernohan[9] reported a case of congenital megacolon which at postmortem examination had a dilated and hypertrophied colon. These authors described both an absence of Auerbach's ganglion cells and an imperfect formation of the cells. The cells described as imperfect were said to be smaller than normal and vacuolated. Illustrations revealed the cells to be atrophied in the transverse colon with complete absence in the descending colon. That this condition may exist into adult life is well substantiated by numerous articles, among them the case reported by Rosin et al.[10] of a 54 year old physician who had controlled the symptoms since childhood by a nonsurgical regimen. At surgery the ganglia were noted to be absent in the rectum with extensive dilatation and hypertrophy of the entire proximal colon. Other pelvic viscera may be physiologically altered in association with congenital megacolon. Swenson,[11] in an examination of 82 cases treated surgically, reported that about half the patients with megacolon have atonic bladders with increased capacity. In a later report by the same author seven cases of megaloureter were noted which showed at autopsy diminished ganglion cells in the bladder near the ureteral orifices.[12]

Gross examination of the colon in which a functional obstruction occurs due to altered nerve supply usually reveals a terminal constricted segment of colon and a proximal dilated segment. The mucosa may be atrophic, or may reveal shallow ulceration near the zone of constriction. No organic obstruction to the lumen is present, although the lumen is usually filled with inspissated fecal material. The wall of the colon may be 3 to 4 times normal thickness. In eight of the cases here reported, the constrictions occurred in the rectosigmoid or descending colons. Immediately above the constrictions, the colons became dilated through a gradual enlargement over 4 to 6 cm. With dilatation and widening of the lumen to 2 to 3 times the normal diameter, moderate to extreme hypertrophy of the muscularis occurred. Definite hypertrophy of the muscularis was seen as early as four weeks in one case. In the authors' cases the hypertrophy was predominantly within the

circular muscle and was present in both the constricted and dilated segments. When a colostomy was done and when there was a lengthy segment of dilated colon in which ganglion cells were present, the colon just distal to the colostomy was the first to return to normal diameter.

Microscopic examination revealed that the junction of the dilated and constricted portion was not necessarily correlated with the termination of myenteric ganglion cells. In two cases the constricted portion began in the lower descending colon and extended to the anus. There was, however, an absence of ganglion cells extending from the anus well into the transverse colon in one case and through the cecum in another. The surgeon cannot assume that ganglion cells are present in the intestine above the constriction.



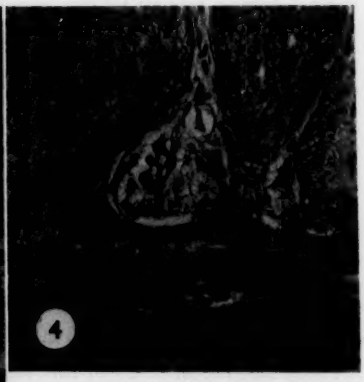


FIG. 3. Photomicrogram taken from dilated bowel near point of constriction. Ganglia are normal in number but show much swelling in periganglionic spaces.

FIG. 4. Another section near zone of agenesis shows distorted cells which are stained deeply by basophilic dyes.

Microscopic examination of the bowel wall is the only way that the presence or absence of ganglia can be established in any given point. The cessation of ganglia occurs abruptly —over a length of 2 to 3 cm. The authors were unable to find definite evidence of an actual decrease in number of cells in the colon proximal to the agenesis. The diminution in numbers of cells was thought to be more apparent than real. The apparent diminution was prevalent in dilated portions of the colon. Doubling or tripling the diameter of the intestine greatly increases the surface area, and thus a limited number of cells distributed over a greater area would suggest diminution of ganglia. In the material abnormal appearing ganglia were present as much as 10 cm. above the area of complete agenesis. The ganglion cells which often lie in nests revealed periangliomic clear spaces within the stroma (Fig. 3). The cells were often smaller than normal and distorted in shape (Fig. 4). Rarely a vacuolation of the cytoplasm was noted. Frequently when cells were noted to lie in nests of 2 to 8 cells, all but one or two of the cells would be small and distorted. When frozen sections of the intestinal biopsies are made, it is important for the pathologist to differentiate between morphologically-appearing normal cells and this frequently-seen zonal margin of abnormal myenteric ganglia.

The segmenting and pendular contractions of the colon are myogenic. Peristaltic contractions, however, are dependent upon the nerve plexuses within the wall of the intestine. Sympathetic and parasympathetic nerves provide extrinsic nerve impulses to the colon. The parasympathetic nerves augment the peristaltic contractions while the sympathetic fibers inhibit the contractions. Vagal innervation of the colon terminates within the first third or half of the transverse segment. The remainder of the colon including the rectum draws its parasympathetic supply from the second, third and fourth sacral nerves. These preganglionic fibers pass to the colon where they synapse with the myenteric ganglion cells of Auerbach and with the submucous plexus of Meissner. The nerves carrying inhibitory supply to the colon (sympathetic) are the first, second and third lumbar. Increased colonic activity follows sectioning of these latter nerves, and their stimulation causes relaxation of the distal colon. Sectioning of the parasympathetic supply to the colon (pelvic nerves) when the sympathetic innervation remains intact produces relaxation of the wall. Stimulation of parasympathetic pelvic nerves produces contraction of both longitudinal and circular muscles. This occurs even after destruction of brain and spinal cord. In the dog, cat and rabbit peristalsis continues after section of all extrinsic nerves (Trumble,[13] Best and Taylor[14]). Any surgical approach aimed at destroying inhibitory impulses to the colon would be directed at the destruction of the lumbar sympathetic supply. The "release" phenomenon thus obtained in man and experimental animals may at first relieve constipation, but often the results are transitory.

Analysis of Cases

In every one of the 10 cases symptoms of vomiting and distention dated from birth and with one exception all infants were admitted to the hospital within the first few days or weeks of life. All had the classical roentgenographic picture of obstruction of the bowel. A number of similar cases seen in earlier years are not included because at autopsy microscopic sections were not made of the constricted segment of bowel. These patients had been explored surgically and because no obstruction was found, were treated medically. All died.

Of this group of 10 cases, one patient, previously explored elsewhere, had peritonitis upon admission and died the following day at 3 weeks of age. Another patient, three days old, was explored surgically. No mechanical obstruction was found and the abdomen was closed. Medical management was vigorously pursued but the patient died at one month of age. In seven patients exploration of the abdomen was performed and a transverse colostomy done at the time or at a later date. Two of these patients were in extremis and died the day after colostomy was performed. Another lived for two months after transverse colostomy and died of malnutrition, infection and dehydration. At postmortem examination the entire colon from cecum to rectum contained no ganglia. The fourth patient died of unrecognized and misinterpreted small bowel obstruction two weeks after colostomy. In some of these patients biopsies of the large bowel at various levels were taken at the time of exploration. Three patients survived transverse colostomy but had stormy courses requiring hospitalization for 2, 5 and 5 months, respectively (see case report).

The tenth patient had classical symptoms of neurogenic bowel obstruction at birth with no bowel evacuation the first three days of life. For no reason at all the bowels began to move normally and continued to do so for five weeks. Then constipation again became severe and required constant stimulation with suppositories and repeated enemas. At

5 months of age the infant was flown in from Guatemala, and proved to be a typical case of congenital megacolon. It was planned to do a Swenson "pull-through" operation but upon exploration of the abdomen a limited segment of the upper sigmoid and lower descending colon only were greatly dilated. Distal to this dilated segment was about 45 cm. of seemingly normal colon. About that time an article had appeared in medical literature advising resection of the isolated dilated segment. Because dilatation was limited to the upper rectosigmoid in seemed a logical procedure in this patient and resection was accordingly carried out and an end-to-end anastomosis performed. The patient did well and its bowels moved freely during a 10 day hospital stay. The parents returned to Guatemala with the child where it continued to do fairly well for about six months when all the previous symptoms returned. The parents brought the child back to our hospital. The clinical picture again was that of classical congenital megacolon. This time the long spastic distal segment of bowel was removed and after freeing the splenic flexure the descending colon was brought down to and anastomosed with the rectal stump. Since this operation a year ago the infant has remained well and is having regular spontaneous bowel evacuations.

The following case report, given in some detail, illustrates the task encountered in caring for three infants upon whom transverse colostomy was performed. All the cases were similar to the one pictured in the case report.

Case Report

C. G., 1 mo. of age, was admitted to Children's Memorial Hospital because of vomiting, constipation and abdominal distention of 1 wk. duration. Her birth weight was 3.0 kg.; highest weight 3.7 kg., and admission weight 3.3 kg. Constipation and abdominal distention appeared immediately after birth. No meconium was passed for 48 hr. Following a few enemas, bowels moved normally and infant was discharged from the lying-in hospital on 10th day in good condition. Until 1 wk. prior to this hospital admission infant thrived and bowel evacuations were normal.

Admission examination revealed a pale, waxy, dehydrated infant with poor tissue turgor. Abdomen was distended and tympanitic. Peristaltic waves could be seen passing from R to L and strong borborgym ending in high-pitched tinkles could be heard. Rectum was empty.

On the 11th hospital day, abdomen was explored surgically through a long, R rectus incision. Distal ileum, cecum and ascending colon were slightly distended, but transverse and descending colon to sigmoid flexure were tremendously distended. From sigmoid flexure to rectum the bowel was of normal size. Wall of distended colon was thick and when handled went into violent contractions.

Fig. 5. C. G. (See case report) At 4 mo. of age, 2 mo. after ileostomy had been done.

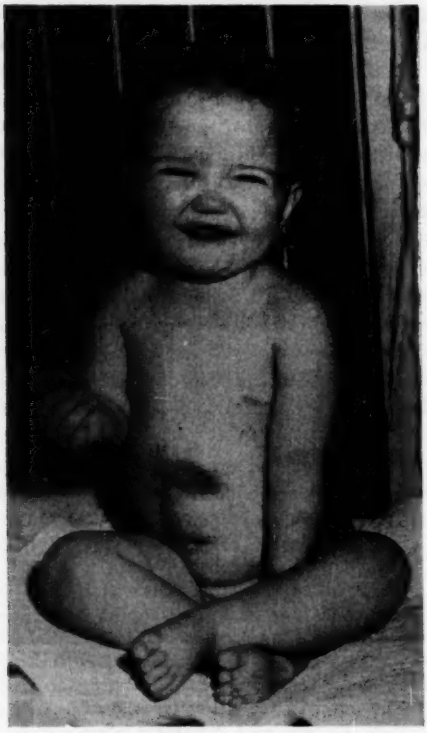


FIG. 6. C. G. At 18 mo. of age, 2 wk. after spastic bowel had been resected and transverse coloproctostomy had been performed.

A large catheter inserted through rectum into the distended bowel resulted in discharge of large amounts of air and feces. Because infant had done well for 4 wk. it was decided not to do a colostomy in anticipation of satisfactory handling medically. That decision was the first error. Distention and vomiting promptly recurred and could not be relieved with enemas.

An ileostomy was done 7 days later through a small muscle-splitting incision and now troubles really began. Infant could not be kept in fluid balance. Plasma CO_2 varied from 28 to 46 vol.%. Infant took a fair amount of food, but slowly lost weight. For a day or 2 she would be bright and vigorous and gain a few grams in weight and then would slip back into apathy and dehydration. Almost constant administration of fluid of some sort was necessary to maintain fluid balance. Injection of Ringer's and/or Darrow's solution into the distal end of ileostomy was of some help. Frequent blood transfusions were given.

Two months later, what had been obvious for a long time became imperative—the ileostomy had to be closed (Fig. 5). Although patient's condition seemed hopeless, the ileostomy was closed and a midtransverse colostomy was done.

Except for an infected wound, 2 attacks of diarrhea, and a pelvic abscess which discharged spontaneously through the rectum, infant did well and was discharged from the hospital, at age of 6 mo., weighing 4.5 kg. Twelve months later she weighed 9.1 kg. and was in excellent health.

This infant was in the hospital 151 days and during this time received: 14 blood transfusions, 105 intravenous administrations of glucose, saline, plasma and amigen; 24 subcutaneous administrations of glucose and saline, and over 11 million units of penicillin, streptomycin and aureomycin.

One year later, after 2 days of terramycin by mouth and cleansing enemas through the distal segment of colon, the following operation was performed: The old R rectus scar was excised and

abdomen opened. Proximal end of colostomy was separated from surrounding structures and could be brought down to the rectum after freeing the hepatic flexure. Remainder of transverse and descending colon and rectosigmoid was then resected. Proximal end of transverse colon was drawn down through rectum and anastomosed to it about 2.5 cm. proximal to the external mucocutaneous line.

The patient made an uneventful postoperative recovery and was discharged 14 days after operation (Fig. 6).

Microscopic examination showed no ganglia in the distal transverse colon, descending colon or rectosigmoid. Earlier biopsy had demonstrated the presence of normal ganglia in proximal end of transverse colon.

In all three patients who survived transverse colostomy the final operative procedure consisted of anastomosing the transverse colon to the rectum and resecting the remainder of the colon. In the other two infants ligation and division of the midcolic artery was necessary to allow the transverse colon to be brought down to the rectum. All are doing well, gaining weight and are having normal bowel evacuations. In spite of the long period of extreme malnutrition no evidence of cerebral retardation has been noted in these infants.

Discussion of Treatment

The various methods of medical management of congenital megacolon in the newborn infant have been tried but all have availed nothing and when continued long enough have lead to disaster. Experience has shown the authors that when a diagnosis of agenesis of the myenteric plexus has been made and the infant shows signs of intestinal obstruction, it will be impossible to carry it along on enemas and suppositories. None of the drugs used, mecholy, syntropan, atropine, did any permanent good. The temporary improvement gained by bowel-emptying with vigorous enemas temporarily seems encouraging but is followed by recurrence of symptoms. In spite of the fact that the bowel is emptied these infants feed poorly, lack vigor, fail to gain weight and slowly decline. Only a few infants can be kept alive for as long as three months.

It is a temptation when operating on these children and finding no mechanical obstruction to yield again and again to the impulse to close the abdomen and hope that the infant can be treated medically for a few months until more definitive surgery can be undertaken, but this never succeeds. It has been the authors' policy until recently to explore the abdomen and upon finding no organic obstruction to have a bystander insert a large catheter through the rectum into the dilated bowel to prove that there is no mechanical obstruction in the lumen of the bowel. Once convinced of this fact, the authors have then proceeded to do a transverse colostomy. Small biopsy section of the constricted bowel and dilated bowel were taken. After ileostomy especially, but even after transverse colostomy, attacks of diarrhea are common and fluid balance is easily upset. The infants eat poorly and have to be helped with repeated blood and plasma transfusions, glucose and saline infusions. In the three children who survived transverse colostomy the hospital stay was long and trying. Transverse colostomy for these infants is not the answer.

The authors now believe the proper procedure for a newborn infant with a diagnosis of agenesis of the myenteric plexus is as follows: The infant is matched for a blood transfusion and one-half unit of 250 cc. of blood is obtained. Regardless of the amount of vomiting the infant has done, the stomach is completely emptied just prior to operation. Open-mask ether anethesia is given and with a tube a steady flow of oxygen is directed beneath the mask. The abdomen is explored and if the diagnosis has been correct a constricted distal segment of bowel will be found with proximal dilatation. If not absolutely

sure that there is no mechanical obstruction within the lumen of the lower bowel, a large catheter should be inserted through the rectum into the dilated bowel. The infant's condition will now determine the next step. If the infant was full term at birth, if its weight is average, its hydration good, and if there are no other congenital abnormalities of note nor any associated complications, resection of the constricted segment of bowel should be done. It is of the greatest importance during the operation to ascertain from biopsy studies of the bowel, made by one who can unmistakably recognize the ganglia of Auerbach's plexus, that the segment of bowel which is brought down to the rectum is neurogenically normal. The zone of constriction between the dilated and constricted bowel is apt not to be the demarcation line between normal and abnormal innervation. It is well immediately to take a biopsy of the constricted zone and another at least 7.5 to 10 cm. proximal to the point of constriction. While the sections are being studied the operation is continued. When it is absolutely established that the proximal segment contains normal ganglia the anastomosis to the rectum is performed.

If the infant's condition does not seem to warrant the definitive operation a colostomy should be done in the dilated bowel. It is desirable to make the colostomy at the point where the pathologist says the ganglia are normal. This point will almost always be in the descending colon or rectosigmoid. In view of the difficulties encountered after transverse colostomies in infants it is advisable, if colostomy is necessary, that it be done in the left half of the colon. After the infant has recovered and is gaining weight normally a suitable time may be chosen for the definitive operation of rectocolostomy. Again, however, it must be established that the distal colon which is brought down has a normal myenteric plexus.

Conclusions

Agenesis of the myenteric plexus or congenital megacolon often manifests itself by intestinal obstruction in the newborn infant. Medical management in such cases is not effective. If the infant's condition warrants, immediate resection of the neurogenically abnormal bowel should be done. In the poor-risk infant sigmoid-colostomy is the procedure of choice.

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SPANISH ABSTRACT

Obstrucción Intestinal en el Recién Nacido por Agenesia del Plexo Mioentérico (Megacolon Congénito)

Los autores hacen un analisis de 10 casos de megacolon congénito en la infancia comentando su sintomatología, diagnóstico, histopatología y tratamiento, enfatizando el cuadro de obstrucción intestinal con que se inicia la enfermedad en el recién nacido.

En todos los enfermos el cuadro clínico se inició con vómitos, constipación y distensión abdominal desde los primeros días de la vida. El vómito de bilis a menudo comienza en el segundo día. La constipación en algunos casos fué absoluta y el recto se encontraba vacío, en otros solo había defecación de escasas cantidades de meconio frecuentemente pastoso y pegajoso; raras veces el tacto rectal motivó la expulsión de meconio normal y gases que aliviaron la constipación por varios días. La distensión abdominal fué también precoz, como si se tratara de una atresia de intestino o recto y a menudo se dibujaban las asas intestinales. La intensidad del cuadro es variable y la evolución también, pues con ayuda de supositorios o enemas puede desaparecer casi totalmente, hasta por una o varias semanas, cuando mas o menos súbitamente recidiva el cuadro añadiéndose deshidratación y mal estado general. Cuando los síntomas son moderados lo único que se sospecha es una constipación ligera y son precisamente los casos que en años posteriores se presentan como enfermos típicos de megacolon congénito.

El error diagnóstico mas común en los enfermos fué el de obstrucción intestinal por atresia del intestino. Clínicamente la presencia en el recto de meconio verde negrusco brillante, aún en pequeña cantidad, es indicación muy a favor de que el intestino está permeable y por eso los tactos rectales frecuentes son muy valiosos. Aun cuando en ocasiones sea imposible hacer un diagnóstico seguro debe tenerse en la mente la posibilidad de una obstrucción neurogénica en cuadros clínicos obstructivos intestinales de estas características y hacer los estudios de rayos X pertinentes.

Los 7 casos que se estudiaron radiológicamente en forma completa, presentaron imágenes de niveles de líquido en las placas tomadas en posición de pie, diagnósticas de obstrucción intestinal y en 3 casos había gas en ambos intestinos y dudoso en 2 casos. La placa simple tomada en decúbito puede ayudar a la localización del sitio intestinal obstruído; en caso de duda un enema pequeño de bario será decisivo para apreciar la localización de los gases y aún el sitio de transición entre el intestino aparentemente normal y el distendido, que aunque generalmente corresponde a donde termina la inervación normal y se inicia la anormal, en ocasiones un segmento considerable de intestino distendido no contiene ganglios nerviosos.

Se ha demostrado definitivamente que la enfermedad de Hirschsprung está íntimamente relacionada con la ausencia o disminución acentuada de las células ganglionares del plexo de Auerbach y su formación imperfecta, participando de este defecto, en algunos casos, otras vísceras como el ureter y la vejiga urinaria. La disminución de los ganglios ocurre abruptamente en una longitud de 2 a 3 cms. de intestino, pero no puede asegurarse sino por examen microscópico, donde terminan las células nerviosas y si corresponde o no a la unión de la parte de intestino distendida y la de calibre normal. Esta se localizó, en 8 de los casos, en el segmento recto-sigmoideo o en el colon descendente. Inmediatamente arriba el colon estaba dilatado aún mas de 2 ó 3 veces el diámetro normal, con moderada hipertrofia de la muscularis, aún en las primeras 4 semanas de vida, tanto de la zona dilatada como de la normal.

La evolución y terapéutica de los enfermos fué la siguiente: uno falleció por peritonitis a la edad de 3 semanas y había sido explorado previamente en otro hospital, otro de 3 dias de edad murió al mes después de que la exploración quirúrgica demonstró que no tenía obstrucción mecánica, a pesar de tratamiento médico intenso; en los otros siete casos, explorados quirúrgicamente, en que se practicó

colostomía transversa, 2 murieron al siguiente día pues eran casos "in extremis" otro murió a los 2 meses por desnutrición, infección y deshidratación y al estudio postmorten no se encontraron ganglios en todo el colon y recto; otro murió también por obstrucción intestinal inexplicable y desapercibida, a las dos semanas de la colostomía y los 3 restantes sobrevivieron, después de tener una evolución tempestuosa que puso a prueba todos los recursos médicos aprovechables para salvarles la vida, practicándoseles, finalmente, anastomosis del colon transverso con el recto.

Al último caso se le hizo primeramente resección del segmento dilatado con anastomosis termino-terminal a los 5 meses de edad. Su cuadro clínico era de megacolon congénito desde el nacimiento que se corrigió espontáneamente por 5 semanas y después se trató médicamente sin éxito. A los 6 meses de esta anastomosis y de evolucionar mas o menos bien, se instala nuevamente el cuadro y se le practica entonces extirpación del segmento distal espástico del intestino y anastomosis del colon descendente con el muñon rectal. Un año después aún se encuentra bien con evacuaciones espontáneas regulares.

Los autores, de acuerdo con la experiencia de estos casos, recomiendan la siguiente conducta terapéutica: 1) No arriesgar la vida del lactante esperando buenos resultados del tratamiento médico, 2) Si el estado general lo permite, hacer la resección del segmento del intestino contraído, cerciorándose por medio de biopsias durante el acto quirúrgico de que la sección proximal del intestino se haga en el sitio donde exista plexo de Auerbach normal, y suturando este extremo al recto. Recomiendan que se haga biopsia en el sitio donde se inicia la distención de intestino y a 3 ó 4 pulgadas arriba de éste. 3) Si las condiciones del niño no lo permiten se hará colostomía en el sitio donde el patólogo indique que existen ganglios normales preferentemente en la mitad izquierda del colon, dada la evolución de las colostomías transversas, y 4) Tan pronto como el estado general lo permita, reoperar y hacer anastomosis con el recto y resección del resto del colon distal.

707 Fullerton Avenue

NEUROLOGIC MANIFESTATIONS OF INFECTIOUS MONONUCLEOSIS IN CHILDHOOD

By FELIX E. KARPINSKI, JR., M.D.
Cleveland

THE central nervous system complications of infectious mononucleosis have been well described in adults, but there is a singular lack of discussion of the complication in the pediatric literature. Since 1931 when Johansen[1] reported the occurrence of serous meningitis and Epstein and Dameshek[2] described stupor and ptosis in patients with infectious mononucleosis, there have been numerous papers concerned with the neurologic complications. Strangely enough, it remained for Geliebter[3] in 1946 to give the first account of this complication in a child with infectious mononucleosis. He described encephalomyelitis complicating infectious mononucleosis in a 10 year old girl. Thelander and Shaw[4] in 1941 described central nervous system involvement in two sisters under 4 years of age. These cases, however, lacked any of the usual features of infectious mononucleosis and the peripheral blood studies suggested infectious lymphocytosis. Piel, Thelander and Shaw[5] make mention of that fact in a subsequent discussion.

The purpose of this paper is to report the occurrence of central nervous system complications in four children with infectious mononucleosis.

CASE REPORTS

Case 1: P. J. B., a 3 yr. old white male child, was admitted to Babies and Children's Hospital of Cleveland with the chief complaint of fever, lethargy and anorexia. The patient was in good health until 6 days before admission when he became apathetic and listless. On the succeeding day there was an increase in apathy and drowsiness associated with a temperature of 39°C. and a pronounced staggering gait. A physician examined the child at this time and noted moderate pharyngitis for which he prescribed a course of sulfadiazine. In the ensuing 4 days the temperature remained elevated and the patient became increasingly apathetic and lethargic. During this time there were occasional complaints of a sore throat. The day before hospitalization, the child lapsed into a semistupor and the temperature rose to 39.5°C.

There was no history of recent immunizations, trauma, exposure to lead or other poisons, and no previous symptoms of incoordination.

On examination the patient was acutely ill and semistuporous. The temperature was 39.6°C. Pulse 130/min., respirations 30/min. and blood pressure 120/70 mm. Forceful stimulation made the patient thrash about aimlessly and his response to commands was poor. There were marked hypotonia and the child could not stand without support. Positive physical findings revealed vertical nystagmus and slight papilledema. There was moderate injection of the pharynx but no exudate or membrane. Moderate nuchal rigidity was present as well as a positive Brudzinski. There was no significant lymphadenopathy or hepatosplenomegaly. The deep tendon reflexes were normal.

Laboratory studies were as follows: RBC count 4.6 million/cmm., Hgb. 12.5 gm./100 cc., WBC count 9.2 thousand/cmm., with a differential count of: segmented neutrophiles 47%, unsegmented neutrophiles 3%, lymphocytes 30%, and atypical mononuclear cells of the Downey type 20%. Platelets were adequate. The heterophil agglutination test was positive in a titer of 1:128. The cephalin flocculation test was negative. Spinal fluid pressure measured 250 mm. of water and there

From the Department of Pediatrics, Western Reserve University School of Medicine, and the Babies and Children's Hospital, Cleveland.

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were 195 cells/cmm., 40% of which were mononuclear cells. Spinal fluid protein was 45 mg./100 cc., and the sugar 89 mg./100 cc. Smears and cultures of the spinal fluid were negative.

An electroencephalographic tracing on the 2nd hospital day showed slow wave delta foci present in the occipital region consistent with meningoencephalitis.

Treatment consisted of aureomycin 250 mg. every 4 hr. for a period of 5 days. Within 12 hr. the temperature had fallen to 38°C. and by 24 hr. the temperature was normal and remained thus. By the 3rd hospital day he returned to rational behavior and his state of consciousness was normal. Atypical mononuclear cells persisted in his peripheral blood smear and still numbered 15% at the time of discharge. A repeat lumbar puncture done on the fifth hospital day revealed a total of 7 cells, 4 of which were mononuclear. The patient gradually regained his strength and was discharged on the eighth hospital day.

Case 2: D. E. C., a 9 yr. old white boy, was admitted to Babies and Children's Hospital of Cleveland with a chief complaint of severe headache, vomiting and fever. The child had been well until 4 days prior to admission, at which time he complained of headache and felt feverish. No temperature determination was made. He received aspirin which apparently gave some relief. On the 3rd day of illness he again developed fever and a violent headache which was followed by bouts of projectile vomiting and severe retching. These symptoms persisted and on the day of admission he developed a morbilliform eruption over the face, bridge of the nose, ears and neck. This eruption was said to be evanescent in character.

On admission the patient appeared well developed, thin and acutely ill. Temperature 38°C. Pulse 100/min. Respirations 20/min. Blood pressure 110/70 mm.Hg.

The positive physical findings included a fine morbilliform eruption over the face, ears and abdomen. The pharynx was moderately injected without evidence of exudate. Generalized shotty lymphadenopathy was present but more marked in the cervical region. A slight degree of nuchal rigidity was present and there were questionable Brudzinski's and Kernig's signs.

The laboratory studies were as follows: RBC count 4.9 million/cmm., Hgb. 13.1 gm./100 cc., WBC count 6 thousand/cmm., with a differential as follows: segmented neutrophiles 41%, unsegmented neutrophiles 1%, lymphocytes 29%, monocytes 2%, basophiles 3%, and atypical mononuclear cells 24%. Platelets were normal. Sedimentation rate 31 mm./hr. (Wintrobe). O.T. 1/1,000 was negative. The heterophile agglutination test was positive in a dilution of 1:128. Routine blood culture was negative. A lumbar puncture revealed a total of 35 cells/cmm., 90% of which were mononuclear. Spinal fluid protein was 76 mg./100 cc. and the sugar 82 mg./100 cc. Smears and culture of the spinal fluid were negative.

Treatment consisted of intravenous fluids and phenobarbital. Within 24 hr. the temperature subsided to normal with disappearance of headache and vomiting. He was completely asymptomatic by the 3rd hospital day and discharged on the 4th hospital day.

Case 3: L. J., a 9 yr. old white male, was admitted to Babies and Children's Hospital of Cleveland with a history of progressive paralysis and lethargy. He enjoyed perfect health until 1 wk. before admission, when he developed a slight fever and nasal discharge. Two days later he complained of headache and a sore throat which was associated with visible cervical lymphadenopathy. These signs and symptoms persisted for the succeeding 3 days, during which time the patient remained up and about. His appetite was not impaired and an occasional aspirin tablet brought some relief from the headache and sore throat. On the 7th day of illness, the patient developed a staggering gait and acted as if he were intoxicated. He was admitted to another hospital the next day with the provisional diagnosis of poliomyelitis and subsequently referred to Babies and Children's Hospital of Cleveland.

On admission the patient was semistuporous and appeared acutely ill. Temperature 37°C. Pulse 116/min.; respirations 30/min. There was definite nuchal rigidity and moderate enlargement of the cervical, axillary and inguinal lymph nodes. The spleen and liver were not palpable. The pupils reacted to light and accommodation and the fundi were normal. The bladder was palpable midway to the umbilicus.

On neurologic examination he was disoriented and responded poorly to simple commands. Marked hypotonia was present and the patient could not sit without support. There was stiff neck and a positive Kernig's sign. The cranial nerves were intact. Abdominal and cremasteric reflexes were absent. The deep tendon reflexes were absent but a positive Babinski sign was elicited on the right. Hand grasp was poor. Abdominal, trunk, and intercostal muscles were extremely weak. The lower

extremities were completely flaccid. There was diminished sensation to touch and painful stimuli distal to T 4-5.

Laboratory studies on admission were as follows: RBC count 4.4 million/cmm., Hgb. 14.0 gm./100 cc., WBC count 10.5 thousand/cmm. with 48% segmented neutrophiles, 7% unsegmented neutrophiles, 11% lymphocytes, 1% eosinophiles and 33% atypical mononuclear cells of the Downey type. Results of a routine urinalysis were normal. The heterophil agglutination test was positive in a titer of 1:1024 and 1:896 after absorption tests with kidney were performed (Davidsohn test). The spinal fluid was under normal pressure, was clear, and showed 36 mononuclear cells/cmm. Spinal fluid protein was 30 mg./100 cc. and the sugar 83 mg./100 cc.

Due to the weakness of the intercostal muscles it was decided to transfer the patient to City Hospital where a respirator was available if needed. There he made a gradual recovery from his acute distress and became more sociable. Repeated catheterization was necessary for urinary retention and recurrent cystitis developed. Gantrisin® and chloromycetin were prescribed for the urinary tract infection. He received physiotherapy daily with gradual improvement except for the paralysis of the lower extremities.

Laboratory studies showed the leukocytes to number 10.4 thousand/cmm., with 36% atypical mononuclear cells in the differential count. A lumbar puncture on the same date revealed 92 mononuclear cells/cmm. and a protein level of 60 mg./100 cc. Examination of the spinal fluid on the 19th and 20th hospital days showed no cells but a protein of 300 mg./100 cc. Two months after admission the spinal fluid protein was 60 mg./100 cc. and there were no cells present. The Davidsohn test on the same date was only positive in a titer of 1:56.

The patient was transferred to a convalescent hospital 2½ mo. after admission and remained there for another 6 mo. Despite continued physiotherapy he made no further improvement and was discharged with paralysis of the lower extremities and persistent urinary incontinence.

Case 4: E. A. W., a 24 mo. old Negro male child, was admitted to Babies and Children's Hospital of Cleveland with a history of fever, anorexia, irritability, lethargy and restlessness of 3 days' duration. The child has been perfectly well until 3 days prior to admission when he became moderately lethargic and felt warm to touch. There were no signs of an upper respiratory infection.

On admission he was found to be well developed and nourished but extremely irritable. Temperature 40°C. Pulse 96/min. Respirations 20/min. Significant physical findings revealed shotty anterior and posterior cervical, axillary and inguinal lymphadenopathy. The submental nodes were also enlarged. The upper respiratory passages were not remarkable. The chest was clear to percussion and auscultation. The liver was enlarged 2 cm. below the costal cage and the spleen was firm and palpable 2 cm. below the costal border. A neurologic examination was essentially negative. There was no nuchal rigidity.

Laboratory studies were as follows: RBC count 3.9 million/cmm.; Hgb. 8.6 gm./100 cc. or 55%; and WBC count 11.5 thousand/cmm. with a differential as follows: segmented neutrophiles 20%, unsegmented neutrophiles 3%, lymphocytes 32%, eosinophiles 3% and atypical mononuclear cells 42%. The heterophil agglutination test was positive in a titer of 1:32. O.T. 1:1,000 was negative. The Kline test was negative. A lumbar puncture revealed a normal pressure with a cell count of 297 mononuclear cells. The spinal fluid sugar was 79 mg./100 cc. and the protein 10 mg./100 cc. Culture of the spinal fluid produced no growth. Agglutinins for typhoid, paratyphoid and Brucella were negative.

Chest RGs were normal, but abdominal views confirmed the hepatic and splenic enlargement. An EEG was interpreted as normal.

The patient was treated with aspirin and alcohol sponges with a drop in temperature to normal on the 3rd hospital day. He was no longer irritable and the hepatosplenomegaly was less noticeable. A repeat lumbar puncture was done on the 7th hospital day which revealed only 5 mononuclear cells. The spinal fluid protein was 15 mg./100 cc. and the sugar 94.8 mg./100 cc. At this time the liver and spleen were no longer palpable and the generalized lymphadenopathy had increased. The patient was more active, alert and afebrile. He was discharged on the 9th hospital day.

Although the heterophil test was only positive in a dilution of 1:32, it was felt that this child had infectious mononucleosis on the basis of the 42% atypical mononuclear cells of the Downey type, the generalized lymphadenopathy, and hepatosplenomegaly. Likewise, the hypochromic anemia present probably did not account for the hepatosplenomegaly since these organs rapidly subsided in size without the benefit of transfusions or alteration in the erythrocyte count and hemoglobin level.

Discussion

It has become increasingly apparent that infectious mononucleosis is not necessarily a relatively benign and self-limited disease. On the contrary, evidence has accumulated in the past few years to indicate that the disease process is a systemic one and its clinical manifestations depend upon the system or systems involved. From the pathologic view there may be as many lesions of infectious mononucleosis as there are organs and tissues of the body, the degree of involvement varying from case to case. Instances of hepatitis, myocarditis, pneumonitis and interstitial nephritis resulting from infectious mononucleosis have been reasonably well documented.

The first clear descriptions of neurologic manifestations associated with infectious mononucleosis appeared almost simultaneously in 1931.[1,2] From 1931 until the present time there have been numerous papers concerned with the central nervous system involvement in this disease. However, as mentioned earlier, few of the published reports have dealt with children, which suggests the possibility that infectious mononucleosis as a cause of central nervous system disease in childhood has been overlooked.

Wintrobe[6] states that headache and blurred vision are the most common complication. Nuchal rigidity, stupor, coma and convulsions[7,8] have been described. Serous meningitis has been observed on several occasions,[9] but the manifestations may be meningoencephalitic[10] or encephalitic. Acute psychosis resembling schizophrenia has been noted by Raymond and Williams.[11] Bilateral papilledema has been described by Piel et al.[5] and Ashworth and Motto.[12] Numerous varieties of ocular palsies have also been reported.[1,2,13,14] Ataxia, believed to be of cerebellar origin, was observed in the case described by Landes et al.[15]

In some instances an acute polyneuritis suggestive of the Guillain-Barré syndrome has been reported in association with infectious mononucleosis.[16–19]

Death from respiratory paralysis has occurred in several cases with neurologic complications and in five of these death was believed to represent central respiratory failure.[13,16,20]

There is no definite order in the appearance of the neurologic symptoms with the usual features of infectious mononucleosis. Signs of central nervous system involvement may appear and subside before the usual manifestations of the disease become apparent. In other cases the lymphadenopathy, peripheral blood and spinal fluid alterations and neurologic symptoms may develop and subside simultaneously. On the other hand, the disease may run its course and subside only to be followed by symptoms of central nervous system involvement.[21]

With involvement of the central nervous system in infectious mononucleosis there may be alterations in the cerebrospinal fluid. These usually consist in an increase of cells and/or protein.[7,15] The pleocytosis is variable but the majority of cells are mononuclear. The spinal fluid sugar and chloride determinations are within normal limits. In some cases, even with maximal disability, the cerebrospinal fluid may remain normal. On the other hand, changes have been found in the spinal fluids of patients with infectious mononucleosis without neurologic symptoms[15,22] (Case 4). Although the heterophil antibody has not generally been detected in the spinal fluid, Silberstein et al.[23] have demonstrated the antibodies in six patients with infectious mononucleosis.

Reports of histopathologic examination of the central nervous system are few but reveal a number of findings.[16,24] These include edema, congestion and mononuclear cell infiltration of the meninges; occasional small perivascular hemorrhages and mild degenera-

tive changes of the brain substance; and perivascular cuffing in the brain and meninges. Cellular infiltration of the cord anterior nerve roots was noted at all levels. Varying degrees of meningitis or encephalitis were demonstrated by Custer and Smith[24] in 3 or 4 cases in which no neurologic symptoms were recognized.

Recovery from the neurologic manifestations usually takes place quite rapidly[21] as it did in 3 of the 4 cases described here. Permanent residual manifestations do occur, however. Bernstein and Wolff[7] report complete recovery in 85% of cases over a period of days to several months.

Since infectious mononucleosis is capable of affecting the nervous system with the production of a variable clinical picture and alterations in the cerebrospinal fluid it should be considered in the differential diagnosis of the numerous "idiopathic" encephalitides and meningitides seen in pediatric practice. Blattner[25] has pointed out the similarities of nervous system involvement in epidemic parotitis and infectious mononucleosis. Therefore, competent studies of the peripheral blood and tests for the heterophil agglutinins are essential if an etiologic diagnosis is to be made.

Summary

Four cases of infectious mononucleosis with central nervous system involvement are presented.

The literature pertaining to the neurologic complications in infectious mononucleosis is briefly reviewed.

Recovery is usually relatively prompt and complete but permanent residual manifestations may occur.

Careful peripheral blood studies and tests for the heterophil agglutinins are essential in the etiologic diagnosis of the obscure diseases of the nervous system.

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SPANISH ABSTRACT

Manifestaciones Neurológicas de la Mononucleosis Infecciosa de la Niñez

Este tipo de manifestaciones ha sido descrito en adultos desde hace varios años pero hasta 1946 se hizo el primer relato, en un niño de 10 años, de una encefalomielitis de tal origen.

En este artículo se presenta la historia de 4 casos comprobados de mononucleosis infecciosa cuyos síntomas neurológicos fueron los de apatía, letargia, semiestupor, hipertonía, nistagmo vertical y papiledema ligero, rigidez de nuca y Brudzinski positivo en el primer caso, con presión del líquido cefalorraquídeo de 250 m.m. de agua, con 195 células, 40% mononucleares, con proteínas de 45 mlgs.% y 98% de glucosa. En el segundo niño había cefalea intensa y vómitos con ligera rigidez de nuca y Brudzinski y Kernig dudosos y su líquido cefalorraquídeo tenía 35 células por M^3, y 90% mononucleares, 76 mlgs.% de proteínas y 82 mlgs.% de glucosa. El caso número 3 de 9 años, cefalea, marcha tambaleante, semiestupor, rigidez de nuca, hipotonía que le impedía sentarse sin sostenerlo, reflejos tendinosos profundos ausentes, signo de Babinski en pie derecho, prehensión manual débil, debilidad extrema de los músculos abdominales del tronco e intercostales, extremidades inferiores completamente flácidas, sensibilidad al tacto disminuída y estímulo doloroso distal a T-4-5, y retención urinaria. El líquido espinal tenía presión normal 36 células mononucleares, 30 mlgs.% de proteínas y 83 mlgs.% de glucosa, posteriormente subieron las células a 92, y proteínas a 60 mlgs.%, y en los dos últimos exámenes lo único anormal fueron las proteínas de 300 mlgs.% y 60 mlgs.% sucesivamente. A los 9 meses de iniciado su padecimiento aun persistía la parálisis de miembros inferiores y la incontinencia urinaria. El último caso presentó como síntomas neurológicos, irritabilidad, letargia, inquietud y el examen neurológico fué esencialmente negativo pero la punción lumbar mostró 297 mononucleares por M^3, glucosa de 79 mlgs.% y 10 mlgs.% de proteínas. Siete días después solo tenía 5 mononucleares, 15 mlgs.% de proteínas y 94.8 mlgs.% de glucosa.

Excepción del tercer caso la desaparición del cuadro neurológico se hizo en unos cuantos días. Todos los casos, presentaron reacciones de aglutinación heterófila a títulos diagnósticos excepción del último, en que no obstante se consideró como mononucleosis por tener hasta un 42% células mononucleares atípicas en la sangre, que también estaban presentes en el resto de los enfermos.

Se hace más y más aparente que la mononucleosis infecciosa no es necesariamente una enfermedad benigna y de limitación propia sino un proceso cuyas manifestaciones clínicas dependen del o los sistemas o aparatos afectados e histopatológicamente puede producir tantas lesiones como órganos y tejidos tiene el organismo en grados variables segun el caso. Efectivamente se han visto hepatitis miocarditis, neumonitis y nefritis intersticiales.

La sintomatología o diagnósticos neurológicos señalados en la literatura en casos de adultos, ha sido de cefalea, visión borrosa, rigidez de nuca, estupor, coma y convulsiones, psicosis aguda simulando esquizofrenia, edema de la papila, varios tipos de parálisis oculares, ataxia de origen cerebeloso aparentemente, meningitis serosa o meningoencefalitis o encefalitis y polineuritis aguda sugestiva del síndrome de Guillain-Barré. Varios casos de muerte por parálisis respiratoria se han relatado y en 5 de estos posiblemente fué por síncope respiratorio de origen central.

Los síntomas nerviosos pueden presentares y desaparecer antes de manifestarse los propios de la mononucleosis, o hacerlo simultáneamente con la adenopatía y las alteraciones de la sangre y líquido cefalorraquídeo, o bien puedan presentarse a continuación. El líquido cefalorraquídeo enseña pleocitosis predominantemente mononuclear y proteínas altas, pero puede ser normal aún en casos con invalidez máxima o inversamente pueden estar presentes las alteraciones del líquido y no existir manifestaciones neurológicas. Se ha encontrado también la aglutinación heterófila en el líquido. Las lesiones histopatológicas señaladas son las de edema, congestión e infiltración celular mononuclear de los meninges, pequeñas hemorragias perivaculares ocasionalmente y lesiones degenerativas ligeras de la substancia cerebral, etc. En la médula se ha visto infiltración celular de las raíces de los nervios en los cordones anteriores a cualquier nivel. Puede suceder que haya grados distintos de meningitis o encefalitis sin que existan síntomas neurológicos. Se ha señalado también la similaridad de las lesiones del sistema nervioso con las de la parotiditis epidémica.

La recuperación de estos cuadros generalmente es rápida pero pueden quedar secuelas permanentes; un 85% de los casos recuperan totalmente en un periodo de días a varios meses.

Los autores del artículo insisten en vista de estos hechos que la mononucleosis infecciosa debe considerarse en el diagnóstico diferencial de los numerosos cuadros meníngeos y encefálicos "idiopáticos" que se ven en la práctica pediátrica y si se quiere hacer un diagnóstico etiológico deben practicarse estudios cuidadosos de sangre periférica y reacciones investigando aglutininas heterófilas.

2065 Adelbert Road

RESPIRATORY PATTERNS IN NEWBORN INFANTS AS DETERMINED BY AIRFLOW AND PNEUMOGRAPHIC STUDIES AND THEIR POSSIBLE RELATIONSHIP TO A DEFICIENT VAGAL MECHANISM

By HERBERT C. MILLER, M.D., AND FRANKLIN C. BEHRLE, M.D.
Kansas City, Kans.

HYALINE membranes have been found in 25 to 50% of the lungs of newborn infants dying in the first few days of life and their presence in large numbers has been regarded as a significant factor in neonatal mortality.[1-4] The pathogenesis of these membranes has been variously explained, but no single theory has received general acceptance. In a recent study it was shown that hyaline membranes in the lungs of vagotomized rabbits were similar in appearance, distribution and histochemical reactions to those occurring in the lungs of newborn infants.[5] In the same study a striking parallel was observed between the clinical course of vagotomized rabbits and newborn infants dying with hyaline membranes in their lungs. In both instances there was increasing dyspnea followed by death within a few hours of the vagotomy in the rabbits and the birth of the infants. These observations raised the question as to whether or not the symptoms and pulmonary lesions in newborn infants dying with hyaline membranes in their lungs were also the result of a deficient vagal control of respirations. The present study was undertaken in an effort to answer this question.

Respiratory movements of the chest and abdomen were selected for study, since animal experiments indicated that the activity of the intercostal muscles and diaphragm are considerably affected by vagal stimuli. The vagi not only help regulate the rate and rhythm of breathing through the Hering-Breuer reflex, but also have a considerable effect on the tone of large muscle groups concerned with respiration. Through the phrenic nerves the vagi have a close relationship with the activity of the diaphragm. Motor impulses in the phrenic nerves coincide with the inspiratory phase (vagal afferents) of artificial respiration in the curarized cat as long as the vagi are intact, but the relationship is lost when the vagi are cut.[6] Sectioning of the vagi results in a significant increase in duration of motor discharges in the phrenic nerves.[7] This close correlation between vagi and phrenics evidently does not exist between vagi and intercostal nerves, for Bronk and Ferguson found that vagotomy produced no change in alternating discharges in nerves leading to the external and internal intercostal muscles.[8] Presumably as a result of the relationship between vagal afferents and phrenic efferents, vagotomized animals often show a diminished and irregular activity of the diaphragm,[9, 10] for which the thorax attempts to compensate. The extent to which costal respiration compensates for the decrease in diaphragmatic activity is inconstant, but in part is related to the age of the animal. Coombs and Pike found that vagotomy in young kittens and puppies invariably resulted in gasping, dyspnea and death within a few hours of operation, while adults of these species could survive the procedure indefinitely.[11] According to these investigators respiratory activity

From the Department of Pediatrics, University of Kansas Medical School, Kansas City, Kans.
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at birth consists of a relatively simple mechanism in which vagi and phrenics are the chief afferent and efferent nerves. They concluded that vagal control over movements of the diaphragm is apparently acquired earlier ontogenetically than regulation by any other portion of the afferent system and, as a consequence, loss of vagal control in very young animals is attended by relatively more severe effects than in adults. All texts on pediatrics stress the fact that infants and young children are largely abdominal breathers. It is not known to what extent newborn infants depend on the diaphragm for respiratory exchange, but the analogy between newborn kittens and puppies on the one hand and newborn infants on the other in respect to their dependency on the diaphragm has been of concern to the authors during the present investigation. Interest in this point has been considerably increased by the knowledge that bilateral midcervical vagotomy in newborn puppies leads to the production of pulmonary hyaline membranes like those seen in newborn infants.[12] One other aspect of vagal control of breathing has been of interest in the conduct of the present experiments and that is the effect of the vagi in coordinating the movements of the diaphragm with those of the thorax. Recently Kerr has demonstrated that in the rabbit vagotomy tends to exaggerate the independent action of the thorax in respect to the movements of the diaphragm.[13] He showed that during the expiratory phase there was an increased tendency for the thorax to expand. This additional movement of the chest at times amounted to a second complete contraction during the time the diaphragm contracted once.

Several investigators have recorded the movements of the chest and abdomen in newborn infants,[14–20] but only Howard and Bauer have attempted to record movements of chest and abdomen separately and simultaneously.[18, 19] These investigators were able to show that in many infants chest and abdomen expanded simultaneously, as in the adult, and in other infants the chest contracted as the abdomen expanded, while in some infants the chest was going through both phases while the abdomen was expanding. They concluded that discrepancies in movements of the chest in relation to the abdomen depended on the strength of ribs, cartilage and muscular action of the thorax in resisting diaphragmatic pull. This mechanistic theory for explaining the vagaries of respiration in newborn infants along with an interest in the chemical control of breathing has characterized American thought on this problem. European investigators, on the other hand, have been concerned with the probability that irregularities of respiration in newborn infants resulted from poorly developed control by the respiratory centers in the medulla.[21] They have not, however, extended their observations to the point of evaluating specifically the role of the vagus nerves in the control of respirations in newborn infants.

The present experiments differ from those of previous investigators in several important respects. The movements of the upper and lower chest have been recorded separately and simultaneously with those of the abdomen, as it seemed on direct observation that the upper and lower chest were going through opposite phases of respiration at times. The movement of air in and out of the lungs has been recorded simultaneously with the movements of the chest and abdomen. The recording of the velocity of air flow has been of inestimable help in determining the onset of inspiration and expiration, since the movements of the chest and abdomen were frequently so incoordinated as to preclude determination of these points. All recordings were made electronically, since the authors were interested only in the direction of the movements of the chest and abdomen and air flow and not in the force of the movements or quantity of air flow. Finally, the recordings have been made on paper moving at speed of 50 mm./second; this was of importance,

since slower speeds often failed to clarify relationships between air movement and muscle activity, particularly if respirations were rapid, as was usually the case.

Methods and Technics

Movements of the chest and abdomen and the velocity of air-flow were recorded simultaneously by a 4-channel Sanborn Poly-viso Cardiette®. Three corrugated, noncollapsible, hollow rubber tubes were wrapped about the infant's torso at 3 levels, (1) just above the umbilicus, (2) just below the nipples and above the xiphoid and (3) as high on the chest as possible. Infant was placed supine on a mat of blankets of about the same width as the baby, so that the corrugated rubber tubes circled the mat posteriorly and the baby's bare skin anteriorly and laterally. The tubes fitted the skin of the baby's torso lightly enough so as not to interfere with breathing in any way and tightly enough to give a good recording. The baby's head extended over the edge of the mat of blankets in a comfortable position to allow easy ingress and egress of air. The arms were held extended alongside the baby's head and to prevent contact between the tube and the baby's arms or chin. The movement of air in and out of the chest was recorded by means of an infant face mask which fitted the baby's face comfortably and tightly. In the apex of the mask was placed a screen of fine monel metal wire, either 200 or 400 mesh, in order to provide sufficient resistance to the passage of air, so that a recording of air pressure in the mask could be made, but not sufficient to alter the breathing. A side-arm led off from the mask to a rubber tube which was connected to a microphone made of piezo crystals, which transformed the mechanical energy into electric energy. In a like manner the changes in air pressure produced in the corrugated rubber tubes by movements of the chest and abdomen were transmitted by similar microphones and recorded by the Cardiette.

All recordings were made with the infants asleep and quiet. The ease with which this was accomplished indicated that the apparatus was not a disturbing factor to the babies. Such babies as were disturbed by handling could be readily quieted by giving food or waiting a few moments for them to quiet down. All but 4 infants in the present study were of the Negro race. The apparatus is demonstrated in Fig. 1.

Results

There were 70 infants on whom 114 tests were done. The distribution of the tests according to birth weight and the age of the infants when tested is shown in table 1. Forty-nine tests were done on 44 fullterm infants and 65 records were obtained on 26 premature infants. The birth weights of the 26 premature infants were as follows: 11

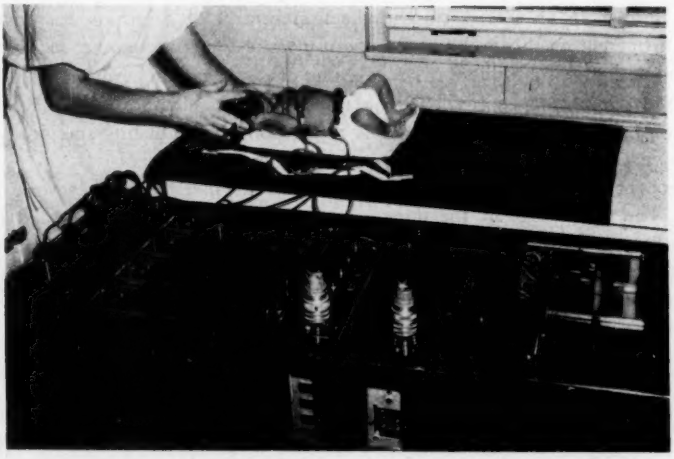

Fig. 1. Corrugated, hollow rubber tubes and face mask in place, connected to individual microphones of piezo crystals and plugged into 4-channel Poly-viso Cardiette®.

TABLE 1

DISTRIBUTION OF 114 TESTS ACCORDING TO AGE AND BIRTH WEIGHT OF 70 INFANTS

No. Infants	Birth Wt. (gm.)	No. tests according to age				Total
		0–24 hr.	2–4 days	5–7 days	8–49 days	
44	2501 or more	15	21	12	1	49
26	2500 or less	15	11	9	30	65
70		30	32	21	31	114

infants weighed between 2001 and 2500 gm., 9 infants were from 1501 to 2000 gm. and 6 between 1001 and 1500 gm. One premature infant died on the second day of life and at autopsy hyaline membranes were present in the lungs. The record on this infant will be considered separately from those of the surviving infants.

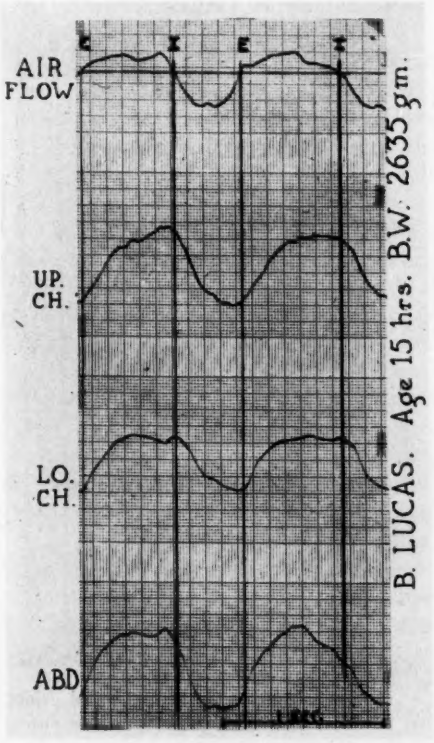

CHART 1. Type 1 respiratory pattern. In this and all subsequent charts, inspiration recorded by downstroke on all 4 tracings; E, beginning of expiration; I, beginning of inspiration; velocity of air flow is zero at E and I; UP. CH., upper chest; LO. CH., lower chest; ABD., abdomen. All 3 pneumographic tracings synchronous with air flow.

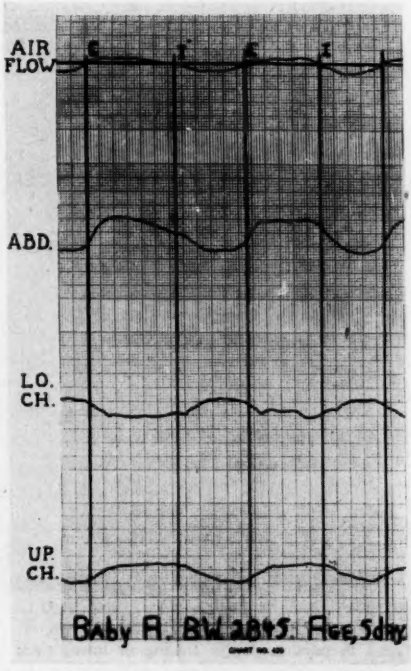

CHART 2. Type 2 respiratory pattern. Pneumographic tracing of lower chest opposite to that of abdomen, upper chest and air flow.

The pneumographic tracings of the surviving infants fell into several well defined patterns. In 54 of the 113 records the tracings of the upper and lower chest tended to be synchronous with that of the abdomen throughout each respiratory cycle and throughout most, if not all, of the record. This pattern has been designated as type 1 and is illustrated in chart 1.

As can be seen in chart 1, the downward deflection (inspiration) of the abdominal tracing occasionally began considerably ahead of the two chest tracings. It was apparent in such instances that the beginning of air inflow was coincident with a sudden acceleration in the downward deflection of the abdominal tracing and not necessarily with its first downward movement. The distribution of type 1 records among the 113 done on 69 surviving infants is shown in table 2. Inspection of table 2 shows that the synchronous pattern of respiration was much more frequently encountered in both premature and full-term infants during the first 24 hours of life than at any other subsequent period. Twenty-two out of 29 records obtained on the first day of life showed this type of respiration, while by the 5th to 7th days of life only 8 of the 21 records were of this pattern and in

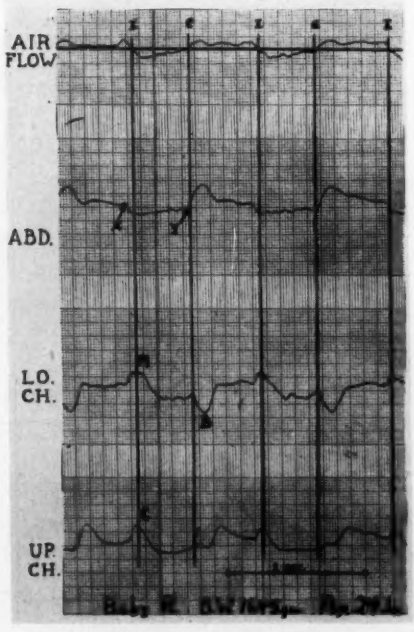

CHART 3. Type 3 respiratory pattern. At A and B, pneumographic tracing of lower chest is opposite to that of abdomen and air flow. At C, which corresponds with A, pneumographic tracing of upper chest is opposite to that of abdomen and air flow.

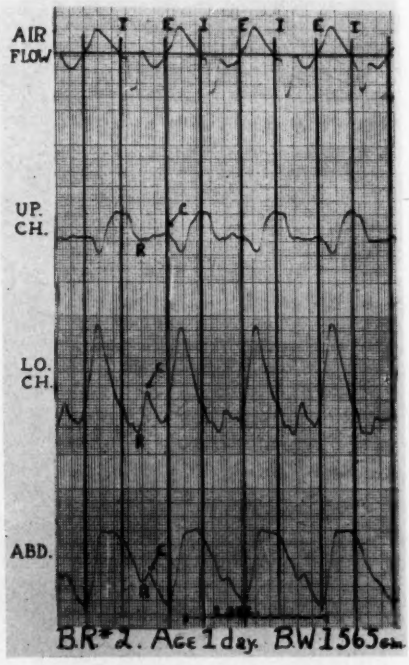

CHART 4. Respiratory pattern of infant dying at 36 hr. of age with pulmonary hyaline membranes. Note sharp drop in air flow velocity during inspiration which occurs as inspiratory movements come to temporary halt at R. Inspiratory movements resume again at C, which in upper chest does not occur until expiration begins as determined by air flow tracing.

TABLE 2

INCIDENCE OF TESTS SHOWING SYNCHRONOUS BREATHING (TYPE 1) ACCORDING TO AGE AND BIRTH WEIGHT OF INFANTS WHEN TESTED

Birth Wt. (gm.)	Tests	Age infant when tested				Total
		0–24 hr.	2–4 days	5–7 days	8–49 days	
2501 or more	total tests	15	21	12	1	49
	type 1	10	9	4	1	24
2500 or less	total tests	14	11	9	30	64
	type 1	12	7	4	7	30
All Wts.	total tests	29	32	21	31	113
	type 1	22	16	8	8	54

the 30 records obtained on premature infants from 8 to 49 days of age there were only 7 with this type of breathing.

In the remaining 59 records there was some dissociation between the movements of the chest, particularly those of the lower chest, and abdomen. In 16 records, although the upper chest and abdomen moved in a synchronous manner, the movements of the lower chest were directly opposite to those of the abdomen throughout the respiratory cycle. This type of breathing is illustrated in chart 2 and has been labelled as type 2. The distribution of these 16 records among the 113 done is shown in table 3. The incidence of this type of breathing was higher among fullterm than premature infants. During the first week of life 13 of 48 records on fullterm infants were of type 2, while only 3 out of 34 records on premature infants exhibited this pattern. This difference, which seemed to exist throughout the first week, was especially notable between the 5th and 7th days of life, when type 2 was found in 5 of 12 records on fullterm infants but in none of the 9 tracings on premature infants. This type of breathing was not common among premature infants at any age, since it was observed in only 3 of the 64 records obtained on premature infants under 49 days of age as compared to an incidence of 13 out of 48 records on fullterm infants less than 8 days old. No tests were made on normal fullterm infants over 10 days of age, as all were discharged from the nurseries by that time.

The next type of record to be described appears to be a variant of type 2. It is illustrated in chart 3. Instead of the movements of the lower chest being directly opposite to those of the abdomen throughout the whole cycle as was the case in type 2, the modification consisted in (1) a brief relaxation of the lower chest and (2) sometimes of the upper chest, both of which occurred just as the expansion of the abdomen began a sudden acceleration, and also (3) a brief contraction of the lower chest, which began just as the abdomen was relaxing. This type of breathing has been labelled type 3 and its distribution is also shown in table 3. There were several variants of type 3, which occurred as follows: a combination of both (1) and (2) was observed in 13 premature and 4 fullterm infants; records in which (1), (2) and (3) occurred together were seen in 9 premature infants and 1 fullterm infant; (2) was the only deviation found in the records of 4 premature and 3 fullterm infants; (1) was found alone in 1 premature and 2 fullterm infants; (3) was the sole alteration in 2 premature and 1 fullterm infant; 1 fullterm infant exhibited a combination of (1) and (3). These variants have been grouped together and considered

TABLE 3

INCIDENCE OF TESTS SHOWING MODIFIED RESPIRATORY PATTERNS (TYPE 2 AND 3) ACCORDING TO AGE AND BIRTH WEIGHT OF INFANTS WHEN TESTED

Birth Wt. (gm.)	Tests	Age infants when tested					Total tests
		0–24 hr.	2–4 days	5–7 days	Total 0–7 days	8–49 days	
2501 or more	total tests	15	21	12	48	1	49
	type 2	3	5	5	13	0	13
	type 3	2	7	3	12	0	12
	types 2+3	5	12	8	25	0	25
2500 or less	total tests	14	11	9	34	30	64
	type 2	1	2	0	3	0	3
	type 3	1	2	4	7	23	30
	types 2+3	2	4	4	10	23	33
All Wts.	total tests	29	32	21	82	31	113
	type 2	4	7	5	16	0	16
	type 3	3	9	7	19	23	42
	types 2+3	7	16	12	35	23	58

as belonging to a single pattern, type 3. In some instances it was difficult to be sure whether a record was to be classified as type 2 or type 3. The incidence of type 3 was much greater among older premature infants than those recently born. During the first 24 hours of life there was only 1 out of 14 records obtained on infants with birth weights of 2500 gm. or less that was type 3, and in the first week of life only 7 of 34 records showed this pattern, while the incidence rose in the period from 8 to 49 days of age to 23 out of 30. Type 3 was also found in 12 of the 48 records done on fullterm infants under 8 days of age.

Assuming that types 2 and 3 were but variants of a single factor modifying the synchronous pattern described under type 1, the incidence of modified respirations was greater among fullterm than premature infants at all stages during the first week of life and the incidence increased in both groups with advancing age. There were 25 out of 48 records obtained on fullterm infants in the first week which showed some alteration in the synchronous pattern, as compared to 10 out of 34 records made on premature infants. Taking both type 2 and 3 records for premature and fullterm infants together, the incidence of modified respirations increased from 7 out of 29 in the first 24 hours of life to 16 out of 32 among infants 2 to 4 days old and then to 12 out of 21 for infants 5 to 7 days of age and finally to 23 out of 31 done on infants between 8 and 49 days old.

One infant not included in tables 2 and 3 had an even different pattern of respirations. Throughout the whole record the movements of both the upper and lower chest were opposite to that of the abdomen throughout the respiratory cycle.

Twenty-one infants had repeated tests done on them. The results are shown in table 4. Infants who had a type 1 pattern on the first day of life tended to show the same pattern on subsequent tests or, if there was a modification, it was towards types 2 or 3, as illus-

trated by cases 4, 11, 16, 17, 18 and 20. The infants who started out with types 2 or 3 on the first day continued to show the same pattern when the test was repeated, as shown in cases 9, 13 and 15. Many of the infants started out with type 1 and some of them continued to show this same pattern on later examinations even though they were done days and even weeks apart, as seen in cases 1, 6, 10, 12 and 14. Occasionally an infant shifted from type 1 to types 2 and 3 and then back to type 1, as illustrated by cases 14, 18 and 21. During a single test an occasional infant would shift its pattern, so that all 3 types were present on the same record, but there was a much stronger tendency for the records to be consistent throughout.

The record on the infant who had hyaline membranes in its lungs at autopsy was obtained at 15 hours of age. The infant had a birth weight of 1570 gm. Cyanosis and retraction of the chest wall did not occur until some hours after the test was done. Rapid respirations had characterized its breathing during the hours preceding the test, and the respiratory rate at the time of the record was 104/min. A sample of the record is shown in chart 4 and warrants special comment, as it was unlike any record obtained on a surviving infant. The striking aspect of the air flow tracing was the rapid, sudden, sharp downward deflection early in inspiration, which indicates thoracic activity.[22] The air flow

TABLE 4

TYPE OF RESPIRATIONS IN 21 INFANTS ON WHOM REPEATED TESTS WERE DONE

Birth Wt. (gm.)	Case No.	Age infant at which tests were done								
		Days			Weeks					
		1	2–4	5–7	2	3	4	5	6	7
2501 or more	1	1			1					
	2		1	1						
	3		1	1						
	4	1	2							
	5	1	1							
2500 to 2001	6		1		1					
	7	1	1							
	8	1		1						
	9		3	3						
	10		1					1		
	11			1	3	3		3		
2000 to 1501	12	1		1		1				
	13	3	2		3	3	3			
	14	1	2		1	1	1			
	15	2		3	3	3				
	16	1		3						
1501 to 1000	17		1		3	3				
	18	1	1		3	3	3	1–3		
	19				3	3		3		3
	20	1		2		3				
	21	1	3, 1–2	1						

N.B. Numbers 1, 2 and 3 refer to type of respiratory pattern.

velocity suddenly diminished following this brief initial peak. This sudden drop in the velocity of the air moving into the chest was synchronous with cessation of inspiratory movements by the upper chest and lower chest and occurred in spite of the fact the abdomen continued to expand at a steady rate. This suggests the actual exchange of air was being made almost solely by the thorax and that the abdomen, although it expanded, was contributing relatively little. Later in the cycle the upper chest expanded sharply just as the abdomen relaxed. This was not observed in any other of the 113 records, but is comparable to the change Kerr described in the thoracic records of vagotomized rabbits.[13]

In some records there was considerable irregularity in the movements of the chest and abdomen. Similar irregularities could be obtained by increasing the respiratory efforts of the infant by administering 10% Co_2 and 90% O_2. It was believed that these occasional irregularities seen in infants breathing ordinary air were related to conditions of stress and restlessness on the part of the infant.

No relationship could be found between the type of respiratory pattern and the sex of the infant or the respiratory rate.

Discussion

The central fact established by the present studies is that the movements of the chest and abdomen, which are synchronous in a large number of infants at birth, are replaced in older infants by a pattern in which the movements of the lower chest and sometimes of the upper chest tend to be opposite to those of the abdomen. The explanation for this opposite movement of the chest probably is only in part related to the strength of the thoracic cage, as suggested by Howard and Bauer.[19] The fact that this pattern of respiration is encountered with greater frequency as the age of the infant increases suggests the possibility that the vigor of diaphragmatic contraction increases with age. It is difficult to believe the thoracic wall becomes less strong as the infants advance in age. The fact that the modified pattern of breathing described as types 2 and 3 in the present study was more frequently encountered in full term than premature infants on the first day of life and at all subsequent periods during the first week after birth suggests that the increase in diaphragmatic strength and tone is related to the maturity of the infant. The tests used in the present study showed only qualitative changes in the respiratory pattern. It is obvious that quantitative measurements which will show the relative roles played by the chest and diaphragm at various ages following birth are necessary before the concept outlined above can be completely established. Such studies are in progress in this laboratory at the present time.

Just as a few infants apparently have the more mature diaphragmatic pattern of breathing (types 2 and 3) established at birth, it is believed that the converse also probably occurs and a few infants perhaps die shortly after birth because of insufficient diaphragmatic activity. The infant who died on the second day of life and a sample of whose respiratory pattern was shown in chart 4 is a case in point. The pneumographic and air flow studies on this infant strongly suggest that the diaphragm was playing a less vigorous role than in any of the other infants studied. According to the authors' present theory this infant was attempting to compensate for the insufficient diaphragmatic action by an increase in its thoracic activity, but for reasons that are not clear the thorax in the newborn infants, as in the newborn kitten and puppy, can not compensate for the impaired activity of the diaphragm. In support of this concept are some clinical observations made on two other infants who died in the first 48 hours of life. The birth weights of these infants were

1300 and 1280 gm. Both were retracting markedly, but the retractions did not appear to be produced by a vigorous pull of the diaphragm, but rather by an exaggerated expansion of the chest. Judging from the slight excursion of the abdominal wall and the feeble pressure made against the hand placed over the epigastrium, the contractions of the diaphragm were grossly impaired. While the upper chest was making exaggerated excursions, the lower chest was being drawn in. When the expansion of the chests of these two infants was inhibited by manual compression, there appeared to be no increase in diaphragmatic activity to compensate for the restricted excursion of the thorax. Both of these infants died; one had hyaline membranes in its lungs and the other did not. The question may well be raised as to whether the presence of pulmonary hyaline membranes is the basic lesion or merely an indication of a more fundamental disturbance, namely, an impaired diaphragmatic activity.

It is evident that retraction of the lower chest in newborn infants is produced by more than one mechanism and has a different significance depending on the mechanism producing it. So far as these observations have gone, the inspiratory retraction of the lower chest seen in the normal healthy infant is an indication that it has developed the more mature type of diaphragmatic respiration. This is a physiologic process and is to be differentiated from that seen in some infants who die in the first few days of life and who may have hyaline membranes in their lungs. Retraction in the latter seems to be caused in some infants at least, by the tremendous efforts made by the thorax. One can observe that instead of the lower costal margins flaring outwards they are actually curled inwards during inspiration and that the diaphragm and abdomen also seem to be exerting little in the way of counteraction to the pull of the upper part of the chest. This is quite the opposite of the physiologic indrawing of the lower chest which probably is produced by the vigorous pull of the contracting diaphragm. Retraction of the lower thorax is a late sign in the infant dying with pulmonary hyaline membranes. It remains to be determined whether the test situation employed in the present study or some modification of it can be utilized as a diagnostic procedure which will permit a clinical diagnosis to be made before retraction sets in.

These preliminary observations on these three infants who died are reported because the opportunity to observe disturbed physiologic patterns in newborn infants in any one clinic is limited and because the authors' explanation for the deaths of these infants needs to be confirmed. A good deal of emphasis has been placed over the years on the aspiration of foreign materials as an explanation for the deaths of many newborn infants and for pulmonary hyaline membranes.[4] By advancing a different theory the authors are not denying the possibility that aspiration of amniotic fluid and other foreign materials may have an integral part in neonatal mortality and the pathogenesis of pulmonary hyaline membranes. However, hyaline membranes have not been produced in live experimental animals by the introduction of amniotic fluid into their lungs and until more substantial proof for the aspiration theory can be established, all theories should be given due consideration.

If subsequent studies confirm this present impression that death in some newborn infants is related to an insufficient diaphragmatic activity, the question naturally arises concerning the etiology of such a disturbance. The results of the very precise animal experiments of Partridge,[23] Adrian[7] and Bronk and Ferguson[8] clearly indicate the relation of vagal afferents to motor discharges in the phrenic and intercostal nerves. The failure of vagal afferents to reach the medullary centers in the brain or an injury to the centers

or along the motor pathways would all have considerable effects on diaphragmatic activity. In favor of the theory that vagal afferents may not reach the respiratory centers in the medulla is considerable evidence suggesting that the newborn infant has in general a poorly developed vagal mechanism. Such notable physiologists as Wiggers[24] and Hoff[25] have pointed out that the rapid heart rate of the newborn infant with subsequent slowing as age advances is an indication that the vagus is playing a lesser role at this period of life than later. The low output of hydrochloric acid by the stomach[26] and the relatively poor peristaltic activity in the stomach and intestines in young infants[27] also suggest that vagal control has not become fully established at birth. Recently in this clinic it was found that the cough reflex could not be elicited in more than a fourth of newly born infants, while it was demonstrable in 90% of infants over a month old.[28] One explanation for these findings could be a failure of vagal afferents from the larynx to reach the proper centers in the medulla. Even more suggestive of an impaired vagal mechanism in this age period than the above is the observation by Cross and Roberts[29] that phrenic nerve stimulation failed to inhibit spontaneous respiration in newborn infants, although both these investigators and Sarnoff and his co-workers[30] found it to do so in the adult. The inhibition of spontaneous respiration when the phrenic nerve is stimulated is in part a reflex phenomenon and is dependent on an intact vagus, since it has been found to disappear after section of the vagus nerves in dogs.[30] It seems quite obvious from the foregoing studies that the comparative role of the vagus in the newborn infant and in subsequent age groups deserves a more careful appraisal than it has hitherto received.

Summary

Pneumographic tracings of the movements of the upper chest, lower chest and abdomen have been recorded individually and simultaneously with the velocity of air flow by means of electronic equipment in 70 newborn infants. A total of 114 recordings were made on infants from zero to 49 days of age and with birth weights of 1000 gm. or more. Most infants during the first 24 hours after birth had a respiratory pattern in which the inspiratory and expiratory movements of the upper chest, lower chest and abdomen were parallel and tended to be synchronous. In a few infants at birth and in most older infants this respiratory pattern was modified. The modification consisted in the lower chest tending to move in a direction opposite to that of the abdomen and upper chest.

The theory has been advanced that diaphragmatic breathing, which is so characterisitc of older infants, is not completely established at birth except in a few infants who perhaps are more mature. In the more mature infant, contraction of the diaphragm probably exerts a pull on the lower chest, causing its indrawing during inspiration. It has been suggested that inability to develop adequate diaphragmatic contractions may be an important factor in the many neonatal deaths that occur in the first few days of life. It has been pointed out that the newborn infant may have a poorly developed vagal mechanism and that this may be one of the factors causing diaphragmatic activity to be inadequate. Observations on three infants who died during the first 48 hours of life are reported which tend to support the theory that vagal deficiency is a possible cause of inadequate diaphragmatic activity, pulmonary hyaline membranes and neonatal death.

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SPANISH ABSTRACT

Patrones Respiratorios Determinados en Niños Recién Nacidos por Medio de Registros Neumográficos y de la Circulación Aérea Pulmonar

Relación posible con las membranas hialinas pulmonares y la mortalidad neonatal

La patogénesis de las membranas hialinas encontradas en el 25 a 50% de los pulmones de recién nacidos muertos durante los primeros días de la vida considerada como un factor de significación en la mortalidad neonatal, no ha sido aun aclarada. Estudios experimentales en conejos vagotomizados muestran membranas hialinas que son similares en aspecto, distribución y reacciones histoquímicas a las que se encuentran en el recién nacido y que el cuadro clínico es igualmente semejante. Dicho hecho plantea la interrogación de si los síntomas y lesiones pulmonares del recién nacido que muere con membranas hialinas en sus pulmones pueden ser causados por control vagal insuficiente de la respiración razón por la cual se llevó a cabo el registro gráfico de los movimientos respiratorios del tórax y abdomen y de la velocidad de la circulación aérea pulmonar en 70 lactantes en los cuales se tomaron 114 registros, 49 correspondientes a 44 recién nacidos a término, y 65 en 26 prematuros.

Se clasificaron en 3 tipos los registros neumográficos. El tipo I estaba caracterizado por sincronismo de los movimientos del tórax con el abdomen a través del ciclo respiratorio completo, y casi en todo el tiempo que duró el registro. Cincuenta y cuatro de los 113 registros presentaron este tipo. En el tipo II había cierta disociación entre los movimientos del tórax, particularmente de la parte inferior y los del abdomen. El tipo III es una variante del II ya que en lugar de que los movimientos de la parte inferior del tórax sean opuestos a los del abdomen a través de todo el ciclo, se presenta una breve relajación de la parte inferior del tórax o de su parte superior, precisamente en el momento en que se acelera en forma súbita la expansión del abdomen o bien una contracción de la parte inferior del tórax cuando se inicia la relajación del abdomen.

Además, se incluyeron en este tipo otras variantes que se registraron en 19 niños a término y prematuros.

El hecho capital que establece este estudio es que el sincronismo de los movimientos del tórax y abdomen que se observa en un gran número de niños recién nacidos (tipo I) es reemplazado en lactantes mayores por movimientos opuestos de la parte inferior del tórax y el abdomen (tipo II), probablemente debido a la acción del diafragma que por su contracción vigorosa, retrae el tórax y su relajación le permite expanderse. Si esta explicación es correcta se puede asumir que a medida que la edad evanza, el tono y fuerza del diafragma aumenta mas rápidamente que el de los músculos intercostales, en otras palabras, la actividad diafragmática no está lo suficientemente desarrollada al nacimiento para vencer la fuerza de los músculos intercostales y como resultado el tórax en su totalidad se expande sincrónicamente con el abdomen. La integridad fisiológica del diafragma es pues un índice del estado de madurez del niño. Por lo tanto, es posible que así como hay niños, aunque pocos, que al nacer tienen el patrón de respiración diafragmática mas maduro (tipos II y III), hay otros que mueren poco después del nacimiento por actividad diafragmática insuficiente. En este estudio, 3 de los niños fallecieron en las primeras 48 horas de vida y por el examen clínico y su registro neumográfico se comprobó la insuficiencia de respiración diafragmática 2 de ellos tenían pesos de 1.300 y 1280 grs., en uno se encontró membranas hialinas en la autopsia, pero en el otro no las había. Puesto que su patrón respiratorio era practicamente igual se antoja pensar si la presencia de membranas hialinas es la lesión básica o simplemente la manifestación de un trastorno mas fundamental., es decir, la insuficiencia respiratorio diafragmática.

La imposibilidad de producir las membranas hialinas en animales introduciendo líquido amniótico en sus pulmones hace sugerir la hipótesis de que la insuficiencia respiratoria diafragmática explique parte de la mortalidad neonatal. Cual sería entonces la etiología de dichos trastornos?.

En vista de numerosos hechos experimentales en animales y características fisiológicas del recién nacido, como su taquicardia, la escasa secreción gástrica de ácido clorhídrico, pobre actividad

peristáltica, ausencia de reflejo tusígeno, puede postularse que el recién nacido tiene un mecanismo vagal muy pobremente desarrollado y que la interrupción anatómica o fisiológica de sus vías aferentes, eferentes o centros nerviosos correspondientes explicaría la insuficiencia de la respiración diafragmática.

Una prueba mas de esta teoría patogénica es la observación de que el estímulos del nervio frénico en el recién nacido no es capaz de inhibir la respiración espontánea tal como sucede si se realiza en individuos adultos. Es pues posible que esta insuficiencia vagal sea la causa de la actividad diafragmática inadecuada, de las membranas hialinas pulmonares y muerte neonatal.

University of Kansas Medical Center

HYPOPLASTIC ANEMIA WITH MULTIPLE CONGENITAL DEFECTS (FANCONI SYNDROME)

By HANS W. KUNZ, M.D.
New York City

FANCONI'S original description in 1927[1] of a familial syndrome characterized by bone marrow hypoplasia together with microcephaly, skin pigmentation, hypogenitalism, hyperreflexia and strabismus in childhood was followed by a number of reports mainly in the European[2-7, 10, 11] but more recently also in the American literature.[8, 9, 12, 13]

It is the purpose of this report to describe additional cases, to present a follow-up on previously published cases and to emphasize an hemolytic component in the pathogenesis of the anemia.

REPORT OF CASES

Investigation of the family history of these patients revealed no abnormalities except that a maternal aunt had an arrested hydrocephalus. The mother had 2 miscarriages prior to the birth of the patients; a third sibling, now a 3 mo. old girl, appeared normal.

Case 1. A. G., male, was born at term after a normal pregnancy weighing 2 kg. At birth several anomalies were observed. He was admitted to Bellevue Hospital at the age of 5½ wk. with a history of progressive enlargement of the head. Weight on admission was 3.2 kg.; the head measured 44 cm. The external auditory canals opened in an unusually low position in relation to the external ear. Both forearms appeared short and curved, the hands were flexed sharply on the forearms and fixed in this position. The thumbs were absent bilaterally. The genitalia were abnormal in that the prepuce was considerably shortened on the ventral aspect of the penis. There was partial syndactylism between the second and third toes bilaterally. Hyperreflexia was present. RGs showed the ulna to be short and curved, the radius, the first metacarpal bone and the phalangeal bones of the thumb totally absent bilaterally. After a few months of observation with an uneventful course apart from the progressive hydrocephalus, he was transferred to another hospital where he died at the age of 17 mo. from obstructive hydrocephalus. Unusual skin pigmentation or hematologic symptoms were never observed.[14]

Case 2. J. G., male, was admitted to Bellevue Hospital at the age of 2½ yr. with the chief complaints of increasing dyspnea on exertion and purpura.

He was born after a normal pregnancy and was noted to have anomalies of his extremities. At 6 mo. it became evident that growth and development were retarded. Hematologic studies at 18 mo. at another hospital showed no abnormalities. Shortly afterwards he developed increasing weakness and for the first time showed ecchymoses on slight trauma, which became progressively more severe. He was therefore admitted to Bellevue Hospital.

Physical Examination: He was poorly developed and pale, and although 2½ yr. of age, had the physical appearance of a 1 yr. old child. He weighed only 8.1 kg. and was too weak to sit up. His voice was hoarse because of a right vocal cord paralysis. Many petechiae and larger hemorrhages were scattered all over the body and a brown skin pigmentation was noted on both axillae, groins, and on the scrotum. The right nipple was smaller than the left. The head measured 42.5 cm., but appeared well proportioned. The eyes seemed small and unusually close together, and a slight convergent strabismus was present. The heart seemed to be slightly enlarged to the left; a moderately harsh systolic murmur and thrill over the pulmonic area was followed by an accentuated second sound and a long blowing diastolic murmur. The testes were undescended and

From the Department of Pediatrics, New York University, College of Medicine, New York City.
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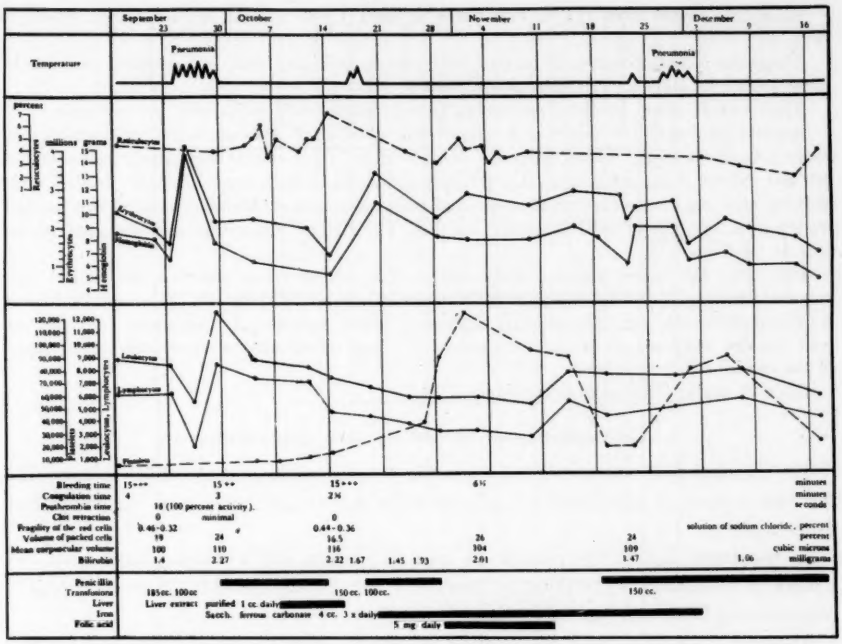

CHART 1. Course in hospital.

the scrotum had a small dimple in the midline. The thumb on the left hand was absent, being represented by a small skin tag on the index finger. On the right hand the thumb had no nail and the distal phalanx appeared deformed. There was also partial syndactylism between second and third toes bilaterally. The rest of the physical examination was normal.

Chest RGs and fluoroscopy revealed a moderate enlargement of the heart to the left and a prominent pulmonary segment with active pulsations. ECGs indicated left and right ventricular hypertrophy. RGs of the hands showed absent first metacarpal and phalangeal bones on the left and an absent distal phalanx of the right thumb. Skull RG showed a shallow sella turcica.

Laboratory Data on Admission: Hgb. was 8.5 gm./100 cc., RBC 2.4 million/cmm. with marked anisocytosis, a tendency to macrocytosis, a slight degree of poikilocytosis and polychromatophilia. The hematocrit was 19%, the mean corpuscular volume 100 cubic micra. There were 4.5% reticulocytes. WBC was 8.8 thousand/cmm. with 30% granulocytes and 70% lymphocytes; the platelet count was 5 thousand/cmm. The bleeding time was markedly prolonged, clotting and prothombin time were normal. Clot retraction did not occur. RBC fragility was normal. The bone marrow showed a marked hypocellularity but with an essentially normal appearance and distribution of the cells, except that no megakaryocytes were seen. Serum bilirubin was 1.4 mg./100 cc.; total serum protein, A/G ratio and fibrinogen were normal. Gastric analysis revealed free hydrochloric acid only after histamine. Mazzini test and urinalysis were normal. Psychometric tests showed a mental age of about 18 mo.

Course in the Hospital (Chart 1): Two transfusions after 1 wk. of hospitalization were followed by fever lasting 6 days during which time Hgb. and RBC dropped again, and there was an increase of the serum bilirubin. After 3 wk. a similar episode occurred. Stool urobilinogen excretion at that time was elevated to 47 mg./day, and the total body hemoglobin was calculated at about 50 gm. Five weeks later the patient had to be transfused again. At this time RBC survival studies were done using 150 cc. of type O,N blood, the patient being type O,M. After 24 days no further agglutination occurred with anti-N substance indicating a definitely shortened survival time.

Serum Na ranged from 127 to 133, serum K from 5.5 to 5.9 and serum Cl from 93 to 96 mEq./1.

Treatment included courses of purified liver extract, folic acid, iron and vitamins, but none of these seemed to influence the hematologic picture.

Three months after admission the patient became progressively worse and died suddenly.

Autopsy Findings: The postmortem examination revealed in addition to the abnormalities already described a patent ductus arteriosus, absence of the right kidney with double ureter on the left and absence of the left testicle. The pituitary, adrenals and testis were all small. Small thrombi showing early organisation occluded a few small pulmonary arteries. Multiple scattered hemorrhages were present over the pericardial surface and there was a larger hemorrhage over the right frontal lobe of the brain.

Histology: The thymus was essentially normal. The adrenal cortex was thin, the cortical cells pale and small, and contained only minimal amounts of lipid in the cytoplasm. Testis and epididymis were normal for the age. The pituitary showed a definite increase of eosinophilic cells and the bone marrow exhibited a moderate hypoplasia of focal distribution with a normal proportion of the various cells.

Cause of death: intracranial hemorrhage.

Discussion and Review of the Literature

The Fanconi syndrome is rare but probably is often unrecognized, which accounts for the few reports in the literature. Undoubtedly some cases have been diagnosed but never reported.

A. Incidence. Up to the present 23 cases, 17 males and 6 females have been described in 14 reports of 16 different families.[1-13, 15] Incomplete data on an additional 3 cases seen by Diamond[16] are also available.

Although Fanconi stressed the familial occurrence, this was found to be true in only 6 families[1, 4-6, 9, 13] with 2 or 3 siblings affected.

Various anomalies in close relatives of patients with the Fanconi syndrome have been reported several times.[1, 4-7, 9, 17]

B. Symptomatology: The main physical findings in cases of Fanconi syndrome are summarized in chart 2.

Hematologic and Serologic Findings: These have never been observed at birth, but usually appeared at 5 to 10 years of age and led to the recognition of the syndrome. Severe anemia, leukopenia with granulocytopenia, and thrombocytopenia were uniformly present; but the most interesting feature was the anemia because of its macrocytosis and hyperchromia. This anemia was considered to be of an aplastic type. But there is also evidence of increased blood distribution, as is shown by unsatisfactory response to transfusions or a rapid fall of the hemoglobin after transfusions[6, 11, 13, 17] (see also Case 2 reported here), elevation of the reticulocyte count, abnormal fragility of the red blood cells in six cases,[4, 7, 9, 11, 13, 17] elevation of the serum bilirubin in five cases[7, 17] (see Case 2) and of the serum iron in four cases.[7, 9, 17] There is also an unusually high excretion of bile pigments in the stools in five patients[7, 9, 17] (see Case 2) which is hard to evaluate in view of other reports of normal excretion[9, 10, 12] but might be understood from Josephs'[18] and Kaplan's[19] observations of depressed urobilinogen excretion after transfusions. Weil,[4] Rohr[9] and Silver et al.[12] were unable to demonstrate autoagglutinins or hemolysins in their patients, examinations which were not carried out in the cases reported here. Dacie et al.,[6] however, found acid hemolysis in one of their patients, and Gasser et al.[17] a weakly positive Coombs and Donath-Landsteiner test in their first case. Both tests were negative in their second case, but again gave a positive result on re-examination of Rohr's second case. The present author found for the first time that

	Sex	Dwarfism	Microcephaly	Skin Pigmentation	Hypogenitalism	Hyperreflexia	Strabismus	Anomaly of Ears	Anomaly of Thumbs	Anomaly of Kidneys	Congenital Heart
Fanconi 1	m	x	x	x	o	x	x	o	o	o	o
2	m	x	x	x	x	x	x	o	o	o	o
3	m	o	x	x	x	o	x	o	o	o	o
Uehlinger	m	(x)	x	x	x	o	o	x	x	x	o
van Leeuwen	m	o	o	x	x	o	o	o	x	x	o
Weil 1	m	o	o	x	x	o	o	o	o	o	o
2	m	o	o	x	x	o	o	o	o	o	o
3	f	o	o	x	o	o	o	o	x	o	o
Hjorth 1	m	o	(x)	x	x	o	o	o	o	o	o
2	f	o	o	o	o	o	o	o	o	o	o
Dacie 1	m	x	o	o	o	o	o	o	o	x	o
2	m	o	o	o	o	o	x	o	o	o	o
Zellweger	m	x	o	x	x	x	o	o	o	o	o
Estren	f	x	o	x	x	o	x	x	x	o	x
Rohr 1	m	o	o	o	o	o	o	o	o	o	o
2	m	o	x	x	x	o	o	o	o	o	o
Gasser 1	m	o	o	x	o	o	o	o	o	o	o
2	f	o	x	x	o	o	o	o	o	o	o
Diamond	m	x		x	x	o	o	o	x	x	o
Brautyman	f	o	(x)	x	o	x	x	o	o	x	o
Baumann	o	x	o	x	x	o	o	o	o	o	o
Silver	f	x	x	x	o	o	x	x	x	o	o
Levy 1	m	o	x	x	o	o	o	x	x	x	o
2	m	o	x	x	o	o	x	o	o	o	o

CHART 2. Summary of findings as recorded by various authors.

in his patient the life time of normal erythrocytes was considerably shortened, a finding which was confirmed by Gasser et al.[17] in Rohr's second case (life time 16 days) and in their second patient (life time 42 days) where they showed in addition a normal survival time of the patient's erythrocytes in a normal recipient. It seems definite from these findings that an extracorpuscular hemolytic mechanism plays a role.

Bone marrow examinations usually revealed a marked hypocellularity with an essentially normal cellular composition; megaloblast and megalocytes have been described by Fanconi[1] only, and Rohr[9, 20] and Gasser et al.[15] were impressed by a medullary reticulofibrosis.

Endocrinologic Findings: It is striking how much the patients with this syndrome resemble each other on the published photographs. Physical findings, such as dwarfism, obesity,[4, 12, 17] enlarged breasts, [12, 17] hypogenitalism and melanin pigmentation of the skin might indicate impaired hypophyseal-adrenocortical function, which is further suggested by the laboratory findings of Gasser et al.[17] of insulin-resistant hyperglycemia with paradoxic response to adrenaline, low ketosteroid excretion, a positive Kepler test and reduced spermiogenesis in a testicular biopsy in Rohr's second case.

C. Prognosis: The outcome has almost universally been fatal. Eighteen of the 23 reported cases died within a few months to a few years after the onset of the hematologic symptoms. A follow-up on the 5 cases which were alive at the time of the respective reports revealed that 2 cases died,[21, 22] one recovered[6, 10] and 2 are alive and their condition is unchanged.[17, 20, 23]

D. Treatment: Iron, arsenical compounds, liver and gastric extracts, folic acid, nucleic acid, vitamin B_{12}, as well as extracts from different endocrine organs have been tried repeatedly without success, except for testicular extract which was used by Weil[4] in his second case. Gasser et al.[17] used cortisone in two patients unsuccessfully. Splenectomy was carried out in 6 cases, and of these 4 died.[3, 8, 12, 16] One case[6] which finally recovered had shown some improvement before splenectomy, and another[9] showed repeated relapses after splenectomy.[7, 17] Blood transfusions were given frequently, but improvement of the anemia did not always follow.

E. Postmortem Findings: Apart from the gross anomalies mentioned above there were no pathognomonic changes described. Whenever endocrine organs were examined they usually appeared normal. An increase of eosinophilic cells was noted in the anterior lobe of the pituitary in this case. The adrenal cortical cells contained reduced amounts of lipid material in Silver's[12] and the second case reported here. Silver et al. also noted necrotic cells in the zona fasciculata and Levy[13] a thin zona glomerulosa with vacuolization of the cytoplasm. On bone marrow examination the hypoplasia found in vivo seemed to be of a focal type and mainly a quantitative one.

F. Etiology and Pathogenesis: Since a history of injury to the fetus was mentioned only twice[8, 12] and since a familial incidence appeared to be quite frequent, most of the manifestations of the syndrome could be explained on a genetic basis. The cause of the pigmentation is unknown. At autopsy the adrenals appeared normal in some instances and abnormal in others, but adequate functional tests have never been carried out, except in Rohr's second case which had a low ketosteroid excretion and a positive Kepler test.[17] The serum electrolytes in the second case are also suggestive of hypocorticism, but unfortunately further investigation of the adrenal cortical function was not done.

Summary and Conclusions

A case of Fanconi syndrome at an unusually young age presenting anemia, leukopenia, thrombocytopenia, microcephaly, hypogenitalism, skin pigmentation, and anomalies of thumbs, kidneys and heart is described. The patient's younger brother with multiple anomalies of the extremities, hydrocephalus, abnormal ears and genitalia died at the age of 17 months without pigmentation and hematologic symptoms, changes which usually do not occur before the age of 5 years.

The literature is reviewed and a follow-up on previously reported cases is given. It seems that in addition to a hypoplasia of the bone marrow an extracorpuscular hemolytic mechanism plays a role in the pathogenesis of the anemia. It is suggested that some manifestations may be due to impaired adrenocortical function.

ACKNOWLEDGMENTS

Data from the first hospitalization of the second patient were obtained from Dr. B. Kramer, Jewish Hospital of Brooklyn, N.Y. Laryngoscopic examination was performed by Dr. J. F. Daly, Bellevue Hospital. The pathologic and histologic examinations were reviewed by Dr. S. Wilens, Bellevue Hospital.

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SPANISH ABSTRACT

Anemia hipoplástica con defectos congénitos múltiples (Síndrome de Fanconi)

Se relata un caso fatal de un niño de 2½ años con síndrome de Fanconi que se manifestaba por anemia, leucopenia, trombocitopenia, microcefalia, hipogenitalismo, pigmentación de la piel y anomalías de los pulgares, riñones y corazón, cuyo hermano más joven murió a los 17 meses,

también con múltiples anomalías de las extremidades, hidrocefalia, oídos y genitales anormales pero sin pigmentación dérmica y síntomas hematológicos como su hermano, síntomas que generalmente no se presentan antes de los 5 años.

La revisión del autor de 23 casos registrados en la literatura demuestra que 17 eran varones y 6 mujeres y pertenecían a 16 familias diferentes habiendo incidencia familiar solo en 6 familias en que 2 ó 3 miembros estaban afectos, aunque anomalías diversas en parientes cercanos han sido frecuentemente reportadas.

Los datos hematológicos permiten hacer el diagnóstico, pero tardíamente, pues estos se presentan por lo común entre los 5 y 10 años de edad. Anemia severa, macrocítica e hipercrómica es característica pero aunque se ha considerado de naturaleza aplástica existe un factor hemolítico importante como lo sugiere la escasa respuesta a las transfusiones, reticulocitosis, fragilidad anormal de los eritrocitos y la bilirrubina, hierro sanguíneo y urobilinógeno fecal aumentados en algunos enfermos. El autor encontró en su caso la supervivencia de eritrocitos normales transfundidos francamente acortada como otros autores lo comprobaron con control, por lo cual es casi definitivo que exista cierto mecanismo hemolítico extracorpuscular. El examen de médula ósea muestra marcada hipocelularidad con una distribución de elementos esencialmente normal, lo cual se manifiesta en sangre por la leucopenia con granulocitopenia y trombocitopenia, pero se han descritos megalocitos y megaloblastos y fibrosis reticular.

En los estudios postmorten de la médula la hipoplasia encontrada in vivo parece ser de tipo focal y principalmente de carácter cuantitativo.

La participación endócrina en el síndrome esta apoyada por los hallazgos de enanismo, obesidad, crecimiento mamario, hipogenitalismo y pigmentación melánica de la piel sugiriendo una hipofunción del mecanismo endócrino hipófisis-adrenocortical que podría explicar la resistencia de la hiperglicemia a la insulina, respuesta paradójica a la adrenalina, excreción baja de Ketosteroides, prueba de Kepler positiva y espermatogénesis disminuida.

El pronóstico es casi siempre fatal; 18 de los 23 casos murieron en meses o pocos años después del principio de los síntomas hematológicos. Se señala solo un caso curado y 2 viven aún pero sin mejoría.

La terapeútica con antianémicos y extractos hormonales, incluyendo la cortisona ha fracasado sistemáticamente. La esplenectomía también falla y el caso que ha curado ya presentaba mejoría antes de realizarla. Las transfusiones sanguíneas no siempre mejoraron la anemia.

La etiología y patogénesis del síndrome puede explicarse sobre una base genética y es posible que ciertas manifestaciones sean debidas a un trastorno de la función de las cápsulas suprarrenales cuya evaluación mas completa debe realizarse.

477 First Avenue

LABORATORY AND CLINICAL STUDIES IN CONGENITAL METHEMOGLOBINEMIA

By HARRY A. WAISMAN, PH.D., M.D., JAMES A. BAIN, PH.D., JULIUS B. RICHMOND, M.D., AND FRANKLIN A. MUNSEY, M.D.
Chicago

METHEMOGLOBINEMIA is a disorder in which a portion of the hemoglobin iron is in the ferric state in unusually high quantities thus limiting adequate oxygen transfer. The congenital form of this disease is relatively rare in contrast to well recognized cases due to a variety of toxic substances and industrial chemicals. The congenital form of the disease may be recognized from birth because of cyanosis or it may be unnoticed for years because the patients have relatively few symptoms if adequate oxygen transfer is accomplished by normal hemoglobin. A number of case reports within the past few years[1-16] have provided information on the hereditary aspects of the disease as well as on the experiences with ascorbic acid or methylene blue as therapeutic agents. The objective of this paper is to provide further information on the disorder from biochemical and clinical data obtained from a 12 year old boy with congenital methemoglobinemia studied over a four year period.

CASE HISTORY

W. P., a 12½ yr. old boy, was admitted to University of Illinois Research and Educational Hospitals because of persistent cyanosis since birth and painful joints for 3 mo. Three days following a home delivery, which was without incident, mother noticed that the baby's skin was blue. During his first month of life patient was hospitalized and received 3 roentgen treatments to chest, presumably for an "enlarged thymus" and following this therapy "blueness appeared to be less." Local physician indicated that "there was something wrong with the heart valve." For the next 10 mo. there appeared to be some decrease in cyanosis and patient continued to do well. Progress was slower than other children but development subsequently was relatively normal.

Present illness began when patient was about 12 yr. of age with 2 or 3 episodes of vomiting and sudden onset of severe pain in midsternal area lasting only a few seconds. Pain occurred during the daytime and would also waken him during the night. Pain disappeared gradually, leaving only a dull ache. Patient was kept in bed for 1 mo. after he began to complain of pain in fingers gradually spreading to elbow. At this time, small lumps were noticed on extensor surfaces of R elbow, R index finger and L great toe. With the exception of swelling of ankles, there had never been any swelling of other joints. Exertional dyspnea had increased in the last 3 mo. There had been occasional spontaneous nose bleeds.

Past history and family history revealed no continuous use of any drug. Since birth, family had always had city water for drinking purposes and in no other member of family was there any history of cyanosis.

Physical Examination: Patient was well developed and nourished and was within the 10 to 25 percentile range for height and weight. Skin had a slate-blue dusky color which was especially apparent in lips, ears and nails. Tonsils were definitely enlarged and cryptic but no pharyngitis was present. Lung fields were clear. There was no neck vein engorgement nor clubbing of fingers. A blowing systolic cardiac murmur was heard best in 2nd L ICS and a harsh blowing diastolic murmur was heard just medial to apex. Second cardiac sound at apex was strong and sharp. P_2 was greater than

From the Departments of Pediatrics and Pharmacology, University of Illinois College of Medicine, Chicago.

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A_2. Blood pressure in arms was 100/66 mm.Hg. and in legs 114/74 mm.Hg. Tip of liver was palpable at R costal margin but spleen was not. Two small firm subcutaneous nodules were palpated on extensor surface of R elbow and extensor surface of R toe.

Laboratory Data: Extensive clinical laboratory data were obtained on patient and most of these were within normal limits.

It was soon apparent from history and cardiovascular observations that patient did have rheumatic fever and rheumatic heart disease, but these were superimposed on congenital methemoglobinemia. Blood was examined spectroscopically and identification of methemoglobin was made by appearance of a well-defined absorption band at 630 mμ. The first methemoglobin determination, as analyzed by Evelyn and Malloy method,[17] revealed that 24% of the hemoglobin was in the form of methemoglobin.

Results

After the diagnosis was established, the patient was kept at bed rest and treated symptomatically for his rheumatic fever. When clinical improvement was obtained, a variety of biochemical and clinical studies was done in order to document the case study. Cornblath and Hartmann[18] had suggested that the low gastric acidity in infants enabled nitrite-producing bacteria to flourish. These bacteria could then convert nitrates in water to nitrites and when the latter are absorbed the cyanosis becomes evident. Early in the study it was of interest to determine whether achlorhydria was present in this patient. Normal gastric acidity was demonstrated, however. A variety of amino- and nitro-containing drugs taken because of abdominal pain was probably the basis for some of the cases of methemoglobinemia in adults. The dubious clinical entity called "enterogenous methemoglobinemia" has been evaluated by both Finch[19] and by Bodansky[20] in reviews on methemoglobinemia.

In order to prove further the diagnosis of congenital methemoglobinemia, methylene

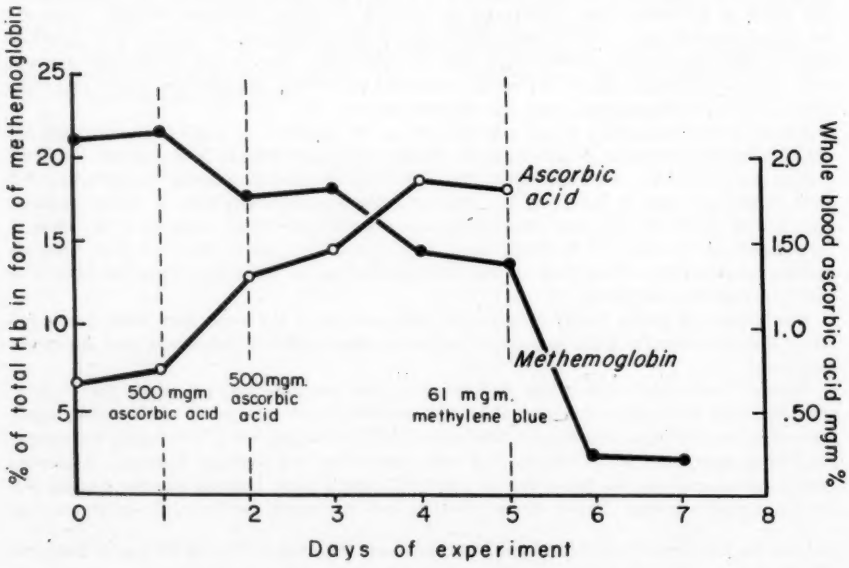

Chart 1. Role of ascorbic acid on methemoglobin level.

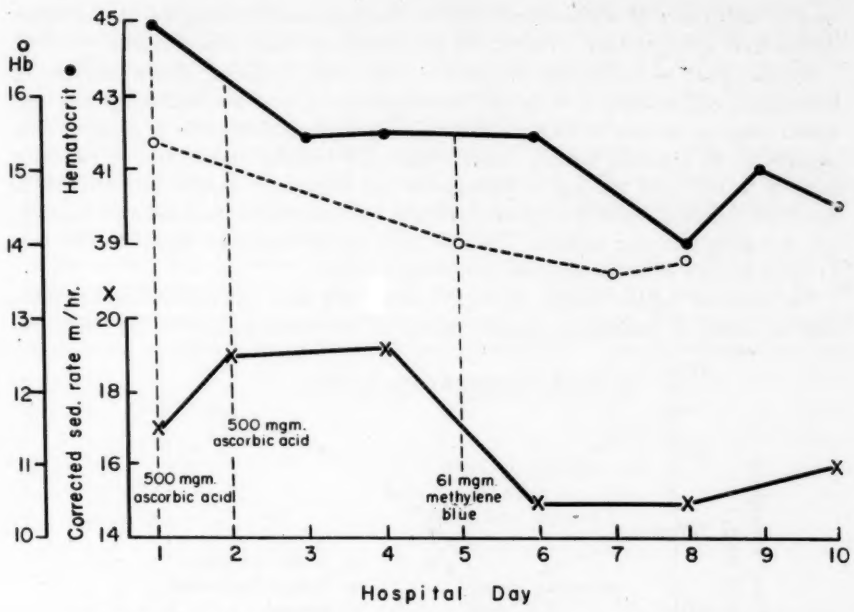

CHART 2. Influence of ascorbic acid on hemoglobin, hematocrit and sedimentation rate.

blue 1.5 mg./kg. body weight was injected intravenously during a five minute period. Within 15 minutes the slate blue appearance of the skin and mucous membranes disappeared and the methemoglobin dropped from a level of 26% to 2%. One month later, the methemoglobin level had risen to 18% without any medication. This regeneration of methemoglobin is therefore at an approximate rate of 0.5%/day. This rate is lower than that reported by Eder et al.[21] and only reflects the variable rate of formation of methemoglobin in these patients.

The observation by Lian et al.[6] that ascorbic acid was effective in reducing methemoglobin to hemoglobin confirmed their hypothesis that the disturbance in the oxidation reduction mechanism of hemoglobin-methemoglobin accounted for the cyanosis. Subsequent work by other investigators has substantiated the quantitative aspects of this phenomenon, using a variety of compounds with a high redox potential.

This patient received ascorbic acid 50 mg. daily for 50 days and the initial level of methemoglobin dropped from 19.5% to 14.6% during that period. This slow fall of methemoglobin level is consistent with the previous findings that the ascorbic acid is less effective than methylene blue.[22] Throughout the initial studies on this patient the blood ascorbic acid values were within normal limits and following the period of ascorbic acid therapy no significant rise was observed. When 500 mg. ascorbic acid was given daily by mouth, greater changes in blood ascorbic acid and methemoglobin levels were obtained as presented in chart 1. It will be seen that the initial blood ascorbic acid value of 0.68 mg./100 cc. blood rises to nearly 2.0 mg./100 cc. three days after two large loses of 500 mg. of ascorbic acid were given on successive days. The methemoglobin levels fell from 21% to 13.7% in that same period. A satisfactory demonstration of the greater effective-

ness of methylene blue is also demonstrated in the chart since it is seen that the methemoglobin level dropped from 14% to 2% after methylene blue administration.

Another point of interest was the effect of large doses of ascorbic acid on the level of hemoglobin and hematocrit. It seemed reasonable that a persistent methemoglobin level would cause an increase in both the hematocrit and hemoglobin levels in order to compensate for the apparent hypoxia. Chart 2 shows the result of another trial of two daily doses of ascorbic acid 500 mg. on hemoglobin and hematocrit. Ascorbic acid was able to lower the slightly elevated hemoglobin level and hematocrit after the amount of functioning oxyhemoglobin was increased, but only after administration of methylene blue was a further decrease in hemoglobin and hematocrit observed.

The increased cardiac output, dyspnea, cyanosis and other clinical findings are probably the result of inadequate oxygen transfer to the tissues because of the methemo-

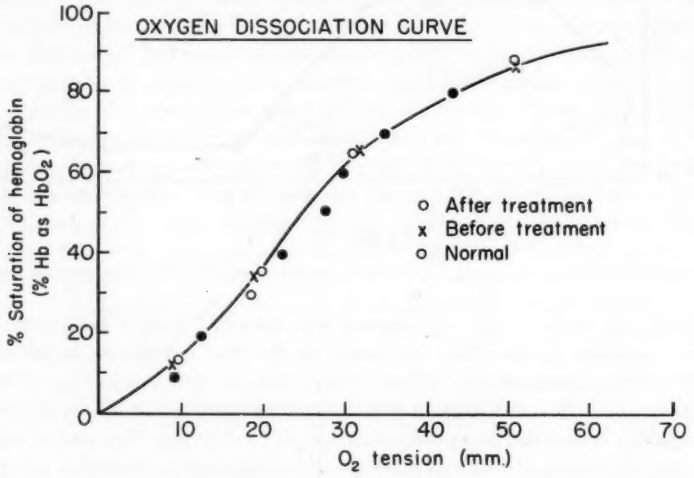

CHART 3. Oxygen dissociation curve of patient before and after treatment with methylene blue compared to calculated normal values.

globinemic blood. It cannot be stated with certainty at what methemoglobin level clinical symptoms will appear. The dissociation of oxyhemoglobin and the cardiovascular mechanisms are brought into play to compensate for handicap of methemoglobinemia. Extensive experiments in animals have been reviewed by Bodansky[20] who claims that the cardiovascular mechanisms are called into play when the concentration of methemoglobin exceeds 40%. Clinical experience indicates that signs and symptoms vary with the methemoglobin level and that between 15 and 20% is the range in which clinical manifestation may become apparent.[20]

In order to obtain definitive information on this point, oxygen dissociation and oxygen capacity determinations were performed.* It will be seen in chart 3 that this patient had a normal oxygen dissociation curve which is in keeping with the data of Darling and Roughton[23] and Litarczek et al.[13] who showed that methemoglobin produces an effect

* Performed by Dr. R. C. Ingraham, Department of Physiology, University of Illinois College of Medicine.

similar to that of carboxyhemoglobin. In agreement with Eder and his co-workers,[21] it was found that the position and shape of the dissociation curve is not altered in familial idiopathic congenital methemoglobinemia. Chart 4 demonstrates the increase in oxygen-carrying capacity of the patient after the injection of methylene blue intravenously. These data are in keeping with the clinical response of the patient.

It should be noted that the patient was able to carry on normal activity in spite of a methemoglobin level of 20 to 26%. This is in agreement with the work of Tepperman et al.[24] who found no apparent effect on oxygenation of working muscle when a cycle ergometer was worked by a subject with 17% methemoglobin.

The authors were interested in the rate at which methylene blue was able to reduce the methemoglobin to oxyhemoglobin. By the use of an oximeter,[25] it was possible to get rapid measurements of the arterial oxygen saturation of the blood. It was also of interest to relate the oximeter readings to the methemoglobin levels. Two experiments were per-

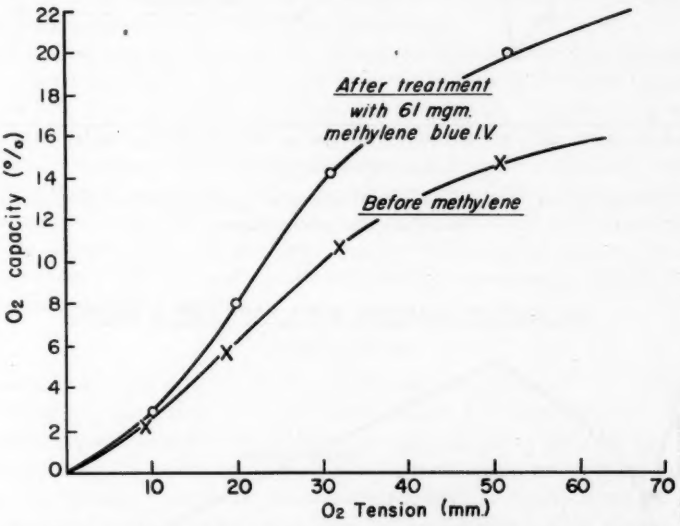

CHART 4. Oxygen capacity in congenital methemoglobinemia before and after treatment with methylene blue.

formed on this patient with the oximeter.* The first experiment was carried out over a 30 minute period and was a measure of the effectiveness of methylene blue to convert methemoglobin to oxyhemoglobin. Chart 5 shows an initial methemoglobin level of 13% and an arbitrary oximeter reading of 56. Methylene blue 61 mg. was given intravenously in the form of a 1% solution over a three minute period, and it will be seen that the oximeter reading dropped at first, but after a five minute period the original oximeter reading was attained. There then followed a rapid rise which was a reflection of the rapid conversion of methemoglobin to oxyhemoglobin. This last observation is confirmed by the decrease in actual methemoglobin to the normal 2% level for this patient.

* With the help of Dr. Marshall Orloff and Dr. C. C. Pfeiffer, Department of Pharmacology, University of Illinois College of Medicine.

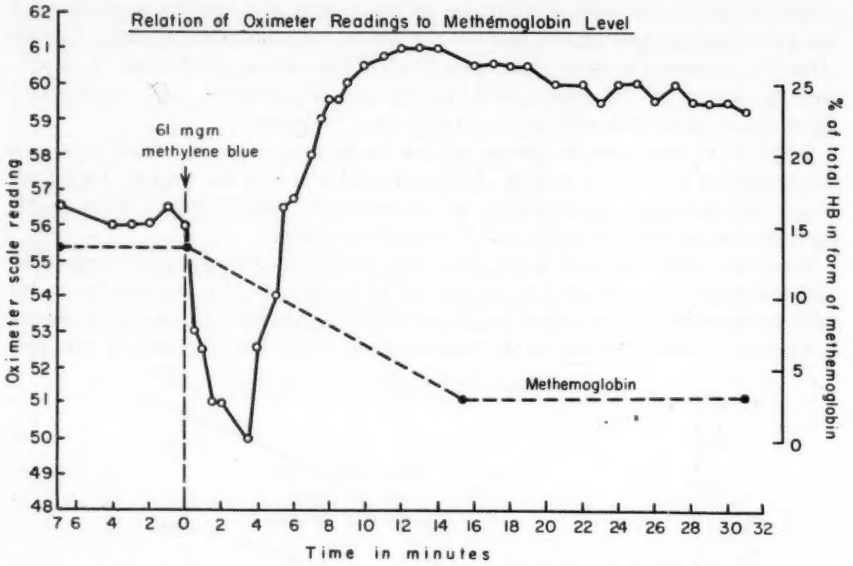
Relation of Oximeter Readings to Methemoglobin Level
61 mgm methylene blue
Methemoglobin
Oximeter scale reading
% of total HB in form of methemoglobin
Time in minutes

CHART 5. Demonstration of increased arterial saturation and reduction of methemoglobin after methylene blue administration.

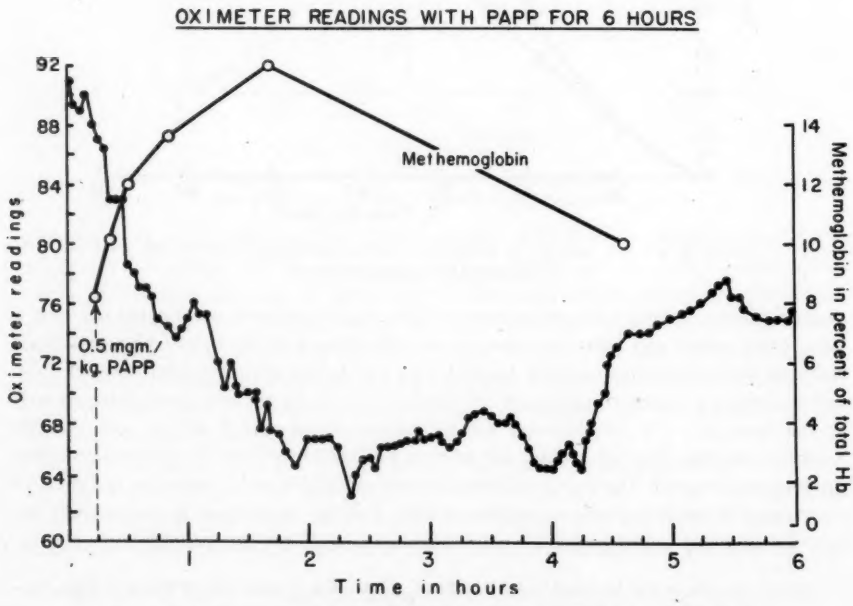

CHART 6. Influence of para-amino-propriophenone on arterial oxygen saturation and methemoglobin level.

The second oximeter experiment was planned so that the administration of a specific, chemical would provide conversion of oxyhemoglobin to methemoglobin. It has been established that when a methemoglobin-forming compound is injected or fed, "methemoglobin accumulates in the blood at a rate characteristic of the compound, attains a maximum concentration at which it remains for a variable period of time, then begins to decrease."[20] Chart 6 illustrates the experiment in which para-amino-propiophenone (PAPP) 0.5 mg./kg. body weight was injected intravenously and oximeter studies done. It was expected that this level of PAPP would oxidize the hemoglobin to the maximum methemoglobin for this particular patient. It will be seen from chart 6 that the oximeter reading falls at once and continues to fall for a period of two hours, becomes stabilized at this low level for another two hours, then begins to rise so that after six hours the arbitrary oximeter units rise to approximately one-half of what they were at the start. The corresponding increase in methemoglobin level indicated the partial effectiveness of the PAPP, but it is of interest that the maximum methemoglobin level of 26% in this patient was not attained by the level of PAPP administered.

It is of interest also that not only did the agent not cause maximum methemoglobin formation in this patient but that after five hours the methemoglobin level began to fall. PAPP had been used extensively on animals but no extensive information on its use in humans was available, and since the dosage was one-half of that used on dogs[26] the methemoglobin maximum was probably not attained in this patient. Evidently some quantitative phenomenon exists, since other experiments with sodium nitrite indicated that adequate amounts of this chemical are also necessary for maximum methemoglobin formation. When sodium nitrite 2.0 gm. were given by mouth to this patient, the cyanosis appeared within 10 minutes and a methemoglobin determination within two hours revealed the maximum level of 26%.

Enzyme Studies

The work by Barcroft et al.[27] Gibson and Harrison[28] and Gibson[29] provided evidence for the hypothesis that a deficiency of co-enzyme factor I in the erythrocytes of patients with congenital methemoglobinemia probably accounted for the symptomatology. The lack of oxygenation of the blood, and the resulting cyanosis could be explained on the inability of the patient's red cells to reduce methemoglobin as rapidly as normal red cells. Further support for the hypothesis was furnished by the report of St. George Breakey, Gibson and Harrison[30] in their study of methemoglobinemic individuals.

The enzymic deficit can be better understood when it is realized that the reduction of methemoglobin is brought about by the following reactions:

$CoIH_2$ (reduced co-enzyme I) + MeHb $\overset{x}{\rightleftarrows}$ CoI (co-enzyme I) + Hb where x represents an unknown enzyme or group of enzymes. An intriguing possibility is that this enzyme is co I-cytochrome c-reductase, but further work is necessary to document this speculation. The presence of methylene blue may cause an increase in the forward rate of the above reaction, but a more likely probability is that it causes the following normally slow reaction:

$CoII.H_2$ (reduced co-enzyme II) + MeHb $\leftrightarrows$ CoII (co-enzyme) + Hb to proceed at a significantly increased rate.

The enzymic studies were undertaken to determine by direct means the rate of oxidation and reduction of co-enzyme I under a variety of conditions in hemolysates from normal and from methemoglobinemic blood.

Enzyme Methods

All bloods were drawn in heparin, chilled, centrifuged, and the red cells washed 3 times with 4 volumes of phosphate-saline (0.01 M phosphate, pH 7.4-0.154 M NaCl) as soon as possible after collection. The washed cells were diluted with phosphate-saline to give 10-14 gm. total hemoglobin/100 cc. All operations on the bloods were conducted at 4° C. with cold reagents. Washed cells were nitrited as described by Gibson.[29] Hemolysates were prepared using the procedure of Guttman et al.[31] in the presence of nicotinamide. Methemoglobin and total hemoglobin were determined by the method of Evelyn and Malloy.[17] Co-enzyme I was prepared and assayed by the method of LePage[32] or obtained from commercial sources* and further purified to at least 70%. Reduced co-enzyme I was prepared either by treatment with hydrosulfite in a manner similar to that described by LePage[32] or by treatment with ascorbic acid as described by Hogeboom and Schneider.[33] Hexosediphosphate was obtained from a commercial source† as the barium salt and converted to the sodium salt before use. All other chemicals were analytic reagent grade and all solutions were prepared using glass-redistilled water. Measurements were made with an Evelyn colorimeter or with a Beckman Model DU spectrophotometer.

Results of Enzyme Studies

In confirmation of the reports of others[21, 29] no difference was found in the oxygen uptake on hexosediphosphate either with or without methylene blue in normal or methemoglobinemic cells in a medium which contained glucose. Hemolysates prepared in the presence of nicotinamide of each type of cell did not show differences in oxygen uptake on hexosediphosphate either with or without methylene blue. The data presented in chart 7 show, however, that there were marked differences in the rates at which normal and methemoglobinemic cells reduce MHb.‡ These data are essentially the same as reported by Gibson[29] with the exception that the present investigators did not observe as great a stimulation by methylene blue when lactate was the substrate. There was considerable variation in rate of different normal subjects and of different samples from a given subject, but in only one case was a normal cell sample ever lower than any methemoglobinemic cell sample.

The authors were unable to demonstrate any "cytochrome-reductase-like" activity in either type of cell using the manometric method suggested by Potter.[34] Many unsuccessful attempts were made using a variety of conditions similar to those employed in the assay of enzymes of the cytochrome chain,[33] to demonstrate a direct oxidation of reduced co-enzyme I (measured by change in absorption at 340 mμ) by hemolysates of either type of blood. Rates were extremely low even when very high concentrations of hemolysate were used. In the light of the experience of other investigators[29, 31] this failure is most disturbing, and the only explanation which comes readily to mind is that since both Gibson and Gutman and their respective co-workers were using relatively impure CoI preparations (30% at best) these may have contained some other necessary co-factor and since the present CoI preparations were at least 70% pure, this system may have been deficient in the hypothetic co-factor. Nevertheless, barring some technical error on the authors' part, there is some reasonable doubt that $CoIH_2$ reacts directly with methemoglobin even in normal cells which are presumably not deficient in flavoproteins.[29]

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* Sigma Chemical Company, St. Louis, or Schwarz Laboratories, Inc., New York City.

† Schwarz Laboratories, Inc., New York City.

‡ Washed cells were nitrated to approximately 50% methemoglobin in all cases and suspended in phosphate-saline to give from 10 to 14 gm. THb/100 cc. 0.2 cc. cell suspension, 0.1 cc. to 10^{-5} methylene blue or buffer, 0.4 cc. 0.1 M glucose or potassium lactate (all in phosphate saline) were pipetted into Evelyn colorimeter tubes and placed in an air incubator with intermittent shaking for 1 hr. at 37° C. Reaction was stopped by addition of 9.0 cc. of 0.02 M phosphate buffer pH 6.0 and MHb and THb determined.[17]

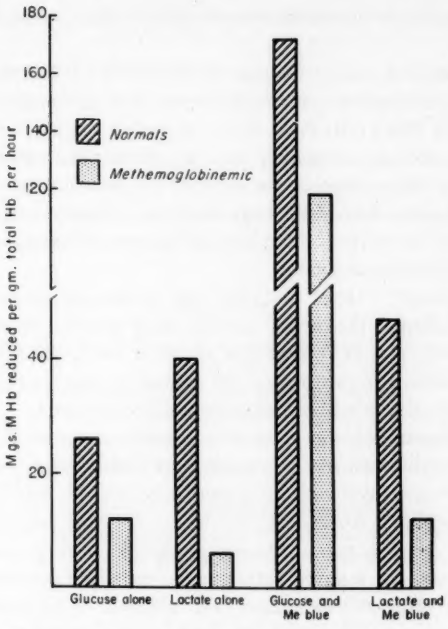

CHART 7. Rate of reduction of methemoglobin by normal and methemoglobinemic cells.

Original MHb levels determined in samples stopped at zero time. "Normals" are average of values obtained from bloods of 7 different normal subjects. "Methemoglobinemic" are average of values obtained from 5 different blood samples from patient during 2 different admissions.

DISCUSSION

The studies reported in this paper are concerned with one of the diseases which can be classified as "inborn errors of metabolism." The circumstance of congenital idiopathic methemoglobinemia is one that requires constant medical attention during the patient's lifetime. Enough information is available at the present time to support the contention that the biochemical defect in the patient's red blood cells is one in which the enzymes controlling the conversion of methemoglobin back to hemoglobin are either absent or are functioning inefficiently. Appropriate medication must be taken by the patient to insure the reduction of methemoglobin to the form of hemoglobin that can provide oxygen to the tissues.

Evidence exists that normal blood has a mechanism by which the slow oxidation of hemoglobin to methemoglobin can be effectively overcome by the enzymes within the red blood cell which can reduce the methemoglobin back to hemoglobin. The concentration of methemoglobin in normal subjects is therefore small and although the quantity of methemoglobin which occurs in different individuals can vary from 0 to 5% the existence of a methemoglobin level above 20% causes the clinical symptoms of polycythemia, breathlessness upon exertion, and the typical slate-blue color. It is of interest that the case reported here had a maximum methemoglobin level of approximately 26%. This level could

not be exceeded despite the administration of sodium nitrite or by the administration of PAPP.

The work of Gibson and his coworkers probably provides the most satisfactory explanation of the enzymic relationships in this particular clinical condition. The reduction of methemoglobin in red blood cells may occur in a manner similar to the reduction of cytochrome and possibly even as a secondary function of the same enzymes. If, then, there is a deficiency of one of these enzymes, for example cytochrome reductase, then the failure of the abnormal cells to reduce methemoglobin at an adequate rate is explicable. In any event these data show the marked differences in the rates at which normal and methemoglobinemic cells reduce methemoglobin.

Gibson and his group[15, 30] have confirmed that methemoglobinemia is inherited as a recessive character. Although the present authors' study on other members of the family is cursory and incomplete, it is of interest that as far as can be determined by history and by examination of immediate relatives of the patient no other case of cyanosis exists in the family. Other more distant relatives were not available for study.

As far as can be determined, this is the first instance of a case of congenital idiopathic methemoglobinemia with concurrent rheumatic heart disease. The course of the congenital illness has in no way interfered with his growth processes and has allowed him to reach the normal growth potential for his age. At the present time he is undergoing the adolescent growth spurt, which is typical for his age period and he performs all normal boyhood activities. The boy has received enteric-coated tablets of methylene blue 60 mg. or ascorbic acid 500 mg. daily and these have been sufficient to maintain normal methemoglobin levels.

The shape of the oxygen dissociation curve is not altered in this case of familial idiopathic congenital methemoglobinemia but certainly the oxygen-carrying capacity is increased after methylene blue is given intravenously or orally. Each patient with this disease probably has an inherently different rate at which methemoglobin is formed in the red blood cells. The authors' experiences with both sodium nitrite and PAPP would be consistent with the view that each patient has his peculiar maximum level of methemoglobin.

Increasing recognition must be given to the fact that specific enzyme deficiencies may account for many of the clinical conditions which at the present time have no definitive etiology. The inborn error of not having a particular enzyme which can function efficiently to reduce methemoglobin to hemoglobin is no more peculiar than that which accounts for the various abnormalities of phenylalanine metabolism such as phenylpyruvic oligophrenia, and tyrosinosis. Only as more studies are undertaken to define the metabolic aberrations which occur in a variety of diseases can we expect to obtain definitive therapy for these conditions.

Summary

Congenital idiopathic methemoglobinemia in a 12 year old boy was corrected by the administration of either ascorbic acid or methylene blue, the latter being more efficient.

The oxygen dissociation curve was normal but as would be expected the oxygen-carrying capacity of the blood was increased after methylene blue was given. Arterial oxygen saturation was determined by an oximeter to demonstrate the increased oxygen-carrying capacity after methylene blue.

Para-amino-propriophenone administration caused an increase in methemoglobin level

but not to the maximum value for this patient. Sodium nitrite by mouth did give the maximum level.

Enzyme studies revealed no difference in oxygen uptake of hexosediphosphate either with or without methylene blue in normal or methemoglobinemic cells in a medium which contained glucose.

No "cytochrome-reductase like" activity was demonstrated in the methemoglobinemic cell.

No definitive evidence exists to support the belief that reduced co-enzyme I reacts directly with methemoglobin in normal cells.

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SPANISH ABSTRACT

Estudios Clínicos y de Laboratorio en la Metahemoglobinemia Congénita

La metahemoglobinemia es un proceso patológico en el que el hierro de la hemoglobina se encuentra en estado férrico en cantidades desusualmente altas limitando así el transporte adecuado de oxígeno. La forma congénita es relativamente rara en contraste con los casos bien conocidos debidos a una variedad de substancias tóxicas y productos químicos industriales. Se caracteriza por cianosis desde el nacimiento que puedo no ser apreciada por años por la escasez de síntomas si el transporte suficiente de oxígeno se hace por la hemoglobina normal.

El caso de los autores fué el de un niño de 12½ años admitido al hospital por cianosis persistente desde el nacimiento y articulaciones dolorosas en los últimos 3 meses. Durante su primer mes de vida se le dió roentgenoterapia por posible hipertrofia del timo y se pensó también en posible lesión valvular del corazón. En los siguientes 10 meses parece que la cianosis mejoró y el enfermo evolucionó bien y su desarrollo, aunque más lento, fué relativamente normal. A los 12 años aproximadamente presentó 2 ó 3 episodios de vómitos y dolor severo súbitamente, localizado a la parte media del esternón que duraba solo escasos segundos. El dolor se presentaba durante el día o lo despertaba en la noche, desaparecía gradualmente quedando solo cierta molestia dolorosa. Después presentó dolor en los dedos que gradualmente se extendió al codo, apreciándose al mismo tiempo pequeñas tumoraciones en la cara posterior del codo derecho, del dedo índice derecho y del dedo grande del pie izquierdo. Excepción hecha de la inflamación de sus tobillos, no tuvo ninguna otra articulación afectada. Tuvo disnea de ejercicio que aumentó en los últimos 3 meses y epistaxis espontánea ocasionalmente. No había en los antecedentes ingestión contínua de droga alguna o consumo de agua distinta de la de la ciudad y no existía otro miembro de la familia con historia de cianosis. El niño estaba bien desarrollado y nutrido su piel tenía una coloración azul pizarra obscura, especialmente aparente en los labios, orejas y uñas. Tenía hipertrofia de sus amígdalas, con criptas, pero no había faringitis. No presentaba datos estetoacústicos pulmonares ni repleción de las venas del cuello o dedos en palillo de tambor. Se oía un soplo sistólico suave en el segundo espacio intercostal izquierdo y un soplo diastólico rudo un poco adentro de la punta del corazón, en donde el segundo tono era fuerte y claro. El cierre de la pulmonar era mas fuerte que el cierre de la aorta. P. A. de 110/66 en los brazos y 114/74 en las piernas. Apenas se tocaba el borde hepático y el bazo no era palpable. Tenía además dos nódulos subcutáneos de consistencia firme en el codo derecho. La mayor parte de los exámenes de laboratorio se encontraron dentro de los límites normales y pronto se hizo aparent por la historia y

las exploraciones cardiovasculares que el enfermo tenía fiebre reumática y reumatismo cardiaco pero que estos procesos se habían sumado a su metahemoglobinemia congénita, pues el examen espectroscópico de su sangre permitió identificar la presencia de metahemoglobina por la aparición de una banda de absorción bien definida en los 630 mμ y su dosificación reveló que el 24% de su hemoglobina era metahemoglobina.

El enfermo se trató con tabletas con capa entérica de azul de metileno, 60 mlgs. diarios ó 500 mlgs. de ácido ascórbico diariamente lo cual ha sido suficiente para mantenerlo con niveles normales de metahemoglobina. En la actualidad el enfermo está atravezando el período de crecimiento rápido de la adolescencia y realiza todas las actividades normales de dicha época.

El caso fué estudiado con ayuda del laboratorio correlacionando sus datos con la clínica y usando distintas substancias para aclarar el mecanismo bioquímico de su metahemoglobinemia haciendo una serie de experiencias que en forma resumida les permite afirmar lo siguiente: a) La curva de disociación del oxígeno fué normal pero como era de esperarse aumentó la capacidad de la sangre para el transporte de oxígeno después de la administración de azul de metileno, lo cual se demostró determinando la saturación de la sangre arterial por medio de un oxímetro. b) La administración de para-amino-propriofenona produjo un aumento de la metahemoglobina pero no alcanzó el valor máximo para el enfermo el cual si se logró con la administración oral de nitrito do sodio. c) Los estudios de enzimas no revelaron diferencia alguna en la toma de oxígeno de hexosadifosfato ya fuera con o sin azul de metileno en las células normales o metahemoglobinémicas en medio con glucosa. d) No se demostró la presencia de actividad reductora semejante a la del citocromo en las células metahemoglobinémicas. e) No existe prueba definitiva para sostener la creencia de que la coenzima I reducida reaccione directamente con la metahemoglobina en las células normales.

1819 West Polk Street

HYDROCOLPOS IN INFANCY AND CHILDHOOD

By LEON ANTELL, M.D.
New York City

HYDROCOLPOS is a clinical condition characterized by the accumulation of fluid, other than blood, in a vaginal canal that is obstructed by an imperforate hymen or by atresia. The condition is rare. It is commonly found in the neonatal period, although it has been reported in older children. Isolated cases have been reported immediately before puberty. It is noteworthy that even in hospitals with large obstetric services and in large pediatric institutions only a few cases have been known to occur.

The subject of hydrocolpos has received only scant consideration in textbooks on pediatrics and gynecology. Barber[1] in his textbook called attention to the fact that hydrocolpos may produce tremendous cystic tumors in the abdomen. Holt and McIntosh,[2] in their chapter on malformations of the female genital organs, devote 1½ lines to the subject.

A recent review of the literature reveals that many cases of hydrocolpos were correctly diagnosed only after exploratory abdominal operations were performed. Twenty-one cases have thus far been reported. In 1904 Commandeur[3] reported a case and this was followed by one reported by Spencer[4] in 1916. In 1940 Kereszturi[5] reported one case of her own and collected seven cases from European literature, one case having been reported as early as 1879. Two of the cases included in her series were in children 6 and 7 years of age. However, in both these children the fluid obtained after incision was fetid pus. During the same year Mahoney and Chamberlain[6] described four cases, and one case each was reported by Bowen[7] (1941), Althoff[8] (1941), Rosenblatt and Woolley[9] (1943), Morris[10] (1945), Maliphant[11] (1948), Leopold[12] (1948) and Sen[13] (1949). The age distribution in the reported cases is of interest. Seventeen cases were reported in the neonatal period and ranged in age from one day to 11 weeks. Two cases were reported at 6 and 7 years of age. However, both of these cases had developed an infection in the hydrocolpos material, and when drained contained fetid pus. It is reasonable to speculate that these two cases very likely had an asymptomatic small or moderate sized hydrocolpos since infancy, and that it only became apparent when the accident of infection was added to a pre-existing condition, analogous to an infection in a pre-existing cyst elsewhere in the body. Two cases occurred just before puberty, one reported by Bowen[7] and the other by Althoff.[8]

CASE REPORT

L. T. L., female, was delivered by forceps and weighed 2.8 kg. at birth. For the 1st 6 days of life no abnormalities were noted. Infant was fed on a standard hospital formula, retained her feedings, and apparently was doing well. Bowel movements and urination were normal. When examined on the sixth hospital day the baby weighed 2.9 kg. On this day the nurse called attention to the fact that the abdomen of the infant was distended.

When the infant was examined by the physician, she appeared comfortable and not particularly ill. She took her feedings well. Temperature was normal. Abdomen was distended and the wall itself showed a pitting edema which reached up to the level of the umbilicus. There was an area of bluish discoloration of the skin, about 5 cm. in diameter, in the left lower quadrant of the abdomen. Right lower extremity was also swollen, with pitting edema throughout. Two small areas of discoloration

From the Pediatric Department of Beth David Hospital, New York City.
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about 2 cm. in diameter were present on the external surface of the right thigh. The discoloration, when noted, appeared to be superficial, like a capillary extravasation of blood under the skin. There was no crepitus and apparently the lesions were not tender to palpation. The edema and multiple ecchimoses presented a bizarre picture, and its exact significance was not clear at this time. Some obstruction of the venous circulation to the lower abdomen and right lower extremity was postulated. Examination of the urine was negative. Blood studies revealed no abnormal findings. Roentgenologic examination of the pelvic bones and of the lower extremities revealed no abnormality.

During the next 24 hr. the infant was closely observed. There was evidence that the pressure on the pelvic vessels was increasing rapidly. The edema rapidly increased and now involved both lower extremities, more markedly on the right. The edema of the abdominal wall had ascended above the level of the umbilicus. Edema at this time was present posteriorly, involving the lower lumbar and sacral regions as well as the buttocks. The edema was so massive that the vulva and anal region was completely engulfed. The skin around the anus was cracked and bleeding, apparently the result of distention of the surrounding tissue. Within 36 hr. after the onset of edema the weight of the infant had increased 0.7 kg. Her general condition was rapidly deteriorating. She refused to take her feedings and began to vomit. She was afebrile. Three days after the onset of her illness the infant failed to void for 15 hr. Accordingly the infant was catheterized and 270 cc. of normal urine was obtained. During the attempt at catheterization a small bulge, the size of a small marble, was noted in the vaginal introitus. It is evident that the bulge represented a distended vaginal canal which was obstructed at its orifice. The true nature of the underlying problem in this infant now became apparent. The hydrocolpos formed a cystic mass which was sufficiently large to obstruct the pelvic circulation. The bulging mass was aspirated and 150 cc. of a moderately thick milky fluid was obtained. Microscopic examination of the fluid showed many WBC and 18 to 20 RBC/hpf. Within a few hours after the aspiration a striking improvement in the condition of the baby was noted. The edema of the lower extremities and abdomen began to recede and vomiting ceased. The infant fed well, voided readily and the bowels moved freely. At the end of 24 hr. after aspiration of the hydrocolpos the condition of the infant was so markedly improved that it seemed well on its way to recovery. The ecchymotic areas receded slowly but progressively without complication. The hydrocolpos was again aspirated 3 wk. later, and 50 cc. of the same type of fluid was obtained. A considerable quantity of fluid kept oozing through the needle puncture. Five weeks after the onset of illness a surgeon incised the membrane and fixed a small rubber tube in the vaginal canal. The tube was removed after 2 days. The child's course proceeded uneventfully after the surgical drainage, and when last seen, at 32 mo., was free from symptoms, and the vaginal opening was patent and adequate.

Discussion

In reviewing the earlier literature dealing with hydrocolpos one gets a definite impression that the sole cause of the obstruction was an imperforate hymen. However, the studies of Mahoney and Chamberlain[6] (1940), based on analysis of autopsy material and careful observation in the operating room, suggest strongly that the obstruction may be due to an imperforate hymen but is more likely due to an arrested development and incomplete involution of the central portion of the vaginal plate. It is a distinct atresia analogous to an imperforate anus or an atresia of the intestine. They call attention to one of their cases in which the obstructing membrane was definitely above the level of the hymen. They also stress the point that the membrane usually seen in hydrocolpos is fairly thick, whereas the hymen is normally thin, and when stretched by retained secretions should even be thinner. The fact that in some of the cases reported the hymen was not even discernible has given rise to some speculation. Mahoney and Chamberlain[6] explain this absence as only an apparent one but not real. When the tissue occluding the vagina is forced down through the hymenal orifice by the pressure of retained secretions, the hymen is flattened out and taken up into the wall of the vagina. They state that it reappears following the incision of the obstructing tissue.

The nature of the retained fluid in the hydrocolpos has been the subject of considerable speculation. The fluid is now regarded as the accumulated secretions of the cervical and

endocervical glands. The cause of the abnormally copious activity of these glands is not definitely established, but it is generally assumed that the glands are stimulated by the estrogenic hormones of the mother. The secretory activity of these glands is presumed to begin in utero, and continue for several weeks after birth.

There are well known clinical facts which tend to substantiate the theories of prenatal and neonatal hormonal activity, namely, neonatal swelling of breasts and vaginal bleeding in the newborn infant. Halban[14] (1904) discussed these phenomena and ascribed them to hormonal reactions, although he had no tangible evidence to prove his view. Since then the hormones in question have been isolated. Philipp[15] and Neumann and Peter[16] have shown that great quantities of estrogenic hormones can be found in the blood of the umbilical cord or in the blood and urine of the newborn infant of both sexes. The fact that these hormones are also found in males suggests their maternal origin. The great variation in the amount of uterine secretion is believed to be dependent upon the degree of estrogen stimulation and the degree of sensitivity of the uterine and cervical glands. Most of the recorded cases fall within one or the other of the two age groups, either during the first few weeks of life, or just before puberty when the estrogenic hormones again awaken the uterine and cervical glands to secretory activity. To substantiate further the view that the genital tract is under the influence of estrogenic hormones during the neonatal period, Mahoney and Chamberlain[6] made histologic studies of the cell structure of the genital tract. They show that during the first month of the infant's life the histologic appearance of the cells of the genital tract resemble that of the adult female. After that the vaginal epithelium changes from the adult type to the thinner, more deeply staining epithelium characteristic of childhood. In 1938 Dobszay[17] was able to reproduce in older infants the clinical, anatomic, chemical and bacteriologic genital conditions that prevail in the first days of life, by administering estrogenic substances in doses of 100,000 to 150,000 units. He, too, was led to the conclusion that the estrogenic hormone of maternal origin physiologically produces the discharge from the vagina of newborn infants. This, together with the known variation of estrin in the urine of pregnant women, appears to account for the variation in the amount of vaginal secretion. This is an important clinical factor in hydrocolpos.

The fluid has variously been described, according to its naked eye appearance, as being, milky, serous, or mucinous, grayish or yellowish gray in color, and in which desquamated epithelial cells are found microscopically. This difference in appearance can be explained by the difference in the state of sensitivity of the uterine and cervical glands towards the hormone, thus contributing different shares towards the chemical, cellular and watery components of the fluid. Commandeur[3] analyzed the fluid chemically and found appreciable quantities of "glucose." It is noteworthy that the vaginal epithelium of adults contains glycogen but, according to Dobszay,[17] it is not found in the vaginal epithelium of older infants and children. The amount of fluid varies from one drachm to several ounces in the neonatal period, and from 0.85 to 2.27 liters in the prepubertal period.

Pathology

The vagina may stretch to enormous proportions producing a cystic mass in the hypogastric region. The uterus may be perched like a cork, at the top of this cystic mass, or may become dilated in the process. The pressure of the fluid may cause stretching and elongation of the urethra at the neck of the bladder. The bladder may be pushed upwards and forwards. The urethra may be obstructed at the urethro-vesical junction, which in turn may lead to dilatation of the bladder, ureters and pelves of both kidneys. There may be

bilateral hydronephrosis or, if infection supervenes, bilateral pyelonephritis. The colon may be displaced upwards and there may be intestinal obstruction. Pressure on the pelvic veins may cause edema of the entire lower half of the body, anteriorly and posteriorly. Rupture of skin capillaries may cause extensive superficial ecchymotic areas.

Diagnosis

1. The symptoms and physical signs are mainly due to pressure of the hydrocolpos upon the pelvic vessels. These pressure symptoms become striking and alarming. There is edema of the lower extremities, first on one side and then on the other, or both may become swollen simultaneously. The lower extremities may become cyanotic. The edema spreads rapidly and involves the abdominal wall, lumbosacral region, buttocks, anal region and vulva, and may reach the level of the umbilicus or above it. Areas of echymosis of the skin may appear. Pressure upon the urethra will produce urinary retention. Edema around the anus may cause an inability to move the bowels. Vomiting may further complicate the bizarre picture. When infection occurs in the genitourinary tract or in the hydrocolpos, then there will be added the usual signs and symptoms of infection of the parts involved.

2. There is a cystic mass in the suprapubic region that does not disappear after catheterization of the bladder. This mass can be outlined by abdominal palpation and rectal examination.

3. Inspection of the vulva will quickly suggest the diagnosis. There is an occlusion of the lower end of the vagina, and a small bulging mass is visible through the vaginal opening, which increases as the infant strains.

4. Aspiration of the bulging vaginal mass will reveal the presence of the characteristic fluid, the disappearance of the suprapubic swelling, and rapid subsidence of the symptoms.

The diagnosis can be substantiated by roentgenogram. The introduction by needle of a radio-opaque substance such as 20 cc. of diodrast into the bulging vaginal mass will reveal the distended condition of the vagina. An equal amount of fluid, or more, must be withdrawn before the injection of diodrast is attempted. The introduction of a 50% dilution of the same radio-opaque substance into the bladder will show the size, shape and location of the bladder, and the status of the uretera and kidney pelves. Roentgenograms are to be taken in the A-P and lateral views.

Differential Diagnosis

Several rare conditions must be considered and excluded. These are: 1. mesenteric, ovarian and urachal cysts, 2. anterior meningocele, 3. tumors, such as embryomas, lymphoblastomas and teratomas.

Prognosis

The prognosis is good when seen early, correctly diagnosed and treated promptly. It becomes much worse when seen late or in the presence of complications or infection.

Treatment

The treatment is simple. It consists of aspiration with a large syringe and a large bore needle as soon as the diagnosis is established. This is to be followed by an incision immediately or some time later when the condition of the infant improves. A drainage tube is to be stitched in situ and left there for several days. When the occlusion is due to atresia of the lower vaginal canal, some sort of plastic operation may have to be undertaken some time later.

SUMMARY

A case of hydrocolpos in an infant 6 days of age is reported with a review of the literature. A new feature, consisting of areas of ecchymosis of the skin, is added. The source and nature of the fluid, as well as the pathology, method of diagnosis, prognosis and treatment of the condition are discussed.

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SPANISH ABSTRACT

Hidrocolpos en la Infancia

Se presenta un caso de hidrocolpos en una niña de 6 días de edad y se hace una revisión amplia del tema. El autor ha reunido de la literatura 21 casos, a los que ha añadido uno mas que motiva el presente artículo. El padecimiento es causado por el acúmulo de líquido en el canal vaginal, obstruido por un himen imperforado o por atresia. Se citan datos experimentales que sugieren que el líquido es el resultado de la actividad secretoria de las glándulas cervicales y endocervicales, estimuladas por las hormonas estrogénicas de la madre que llegan al feto a través de la circulación placentaria. El estancamiento de líquido produce una tumoración quística en la región suprapúbica que puede llegar hasta el ombligo. La tumoración a su vez causa presión sobre las estructuras adyacentes motivando dilatación de los ureteros, hidronefrosis o pionefritis. La presión sobre los vasos pélvicos puede causar edema de las extremidades inferiores o de toda la mitad inferior del cuerpo; ruptura de los capilares superficiales y equimosis. La presencia de un abombamiento del tamaño de una canica en el orificio vaginal, asegura el diagnóstico, que puede ser confirmado por la aspiración de él y estudio a los rayos X después de la inyección de una substancia radio-opaca en la masa quística. El tratamiento consiste en incisión y drenaje del abombamiento del orificio vaginal.

1150 Park Avenue

CAT SCRATCH SYNDROME

By WILLIAM J. WATERS, M.D., SEYMOUR S. KALTER, PH.D., AND JOHN T. PRIOR, M.D.
Syracuse, N.Y.

SEVERAL case reports of a clinical entity related to contact and/or scratches by cats have been made recently. The historical background of this disease has been well covered.[1]

The authors' interest in cat scratch syndrome has been stimulated by the observation of 15 cases among children and adults. The clinical picture manifested by these patients was of such varied nature that further investigation, particularly as regards diagnostic methods, appeared warranted since exact diagnosis could not be established by any single clinical or laboratory procedure. Furthermore, because of certain striking similarities, an attempt was made to group these cases according to a pattern which would be diagnostically significant.

The following cases illustrate the protean nature of the clinical picture. They also serve to point out the features that should lead one to suspect and confirm the diagnosis of cat scratch syndrome:

CASE REPORTS

Case 1. W. H., male, 4 yr. of age. History of cat scratch on L hand with subsequent development of pustule at site 3 wk. prior to onset of fever. Temperature ranged up to 40.5°C. daily and was unaffected by chloromycetin, aureomycin or penicillin therapy given intramuscularly and orally, over a 2 wk. period. On admission, physical findings were an enlarged lymph node in L axilla, about 3 cm. in diameter and somewhat tender to palpation. There was a small healed papule on dorsal surface of L hand. Slight injection of pharynx and uvula was noted (chart 1).

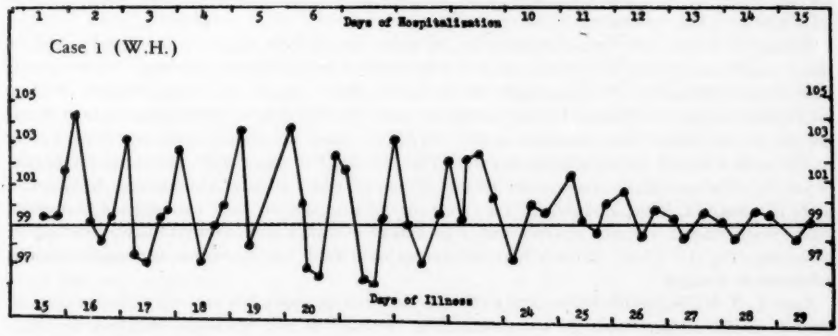

CHART 1

Laboratory Data.—Hematocrit 39%; Hgb. 12.3 gm./100 cc.; WBC count 7.8 thousand/cmm., with neutrophils 57%, lymphocytes 37%, polymorphonuclears toxic, platelets and RBC count normal. Sedimentation rate: 5 mm./hr., urinalysis negative, nose and throat cultures negative, blood (5) negative, chest RG negative, intravenous pyelogram negative. Agglutinations: Typhoid group, negative;

From the Departments of Pediatrics, Bacteriology and Pathology, State University of New York, Medical Center at Syracuse University, Syracuse, N.Y.

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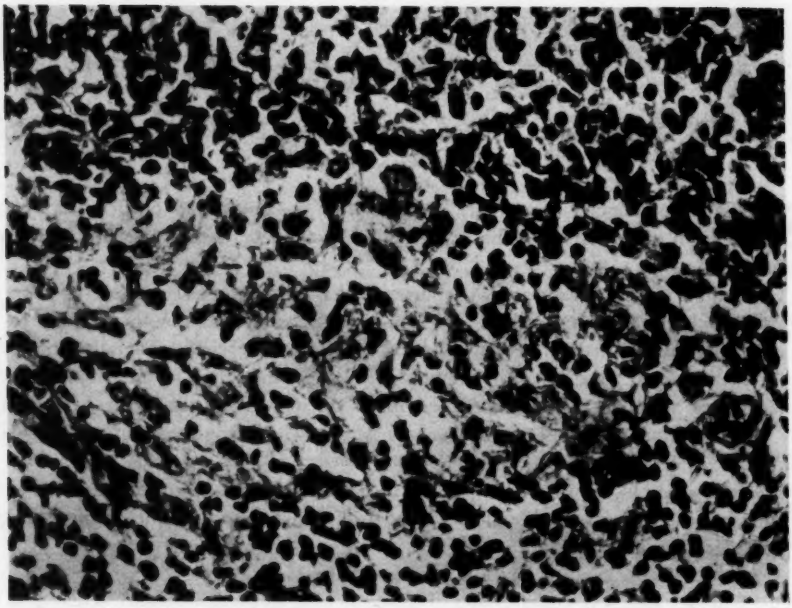

FIG. 1. Case 1. Solitary focus of reticuloendothelial cells. × 450.

Brucella, negative, tularense, negative, Proteus OX-19, negative, Paul-Bunnell, negative, streptolysin titer <50 units, lygranum, positive. Skin tests: O. T. (1:100): negative, Brucella negative, histoplasmin negative, blastomycin negative, Frei antigen negative, cat scratch antigen positive. Lymph node biopsy: solitary granuloma. Culture, negative.

Biopsy of axillary node was performed on 6th wk. of illness. This single axillary lymph node was rather small, measuring 1.5 × 0.2 cm. and was described as being firm in consistency and yellowish-pink on its cut surface. Microscopically, the node revealed a capsule of normal thickness without evidence of cellular infiltration. Cortical lymphoid tissue was hypoplastic with lymph nodules showing no activity within their germinal centers. Medullary cords and sinuses were not unusual with exception of a solitary granulomatous structure. This was ovoid in shape and consisted of an accumulation of reticuloendothelial cells in the central portion of which some edema and rare lymphocytes could be identified. Reticuloendothelial cells comprising the granuloma were characterized by a somewhat spindle-shaped, vesicular nucleus with a prominent nucleolus and indistinct slightly acidophilic cytoplasm (Fig. 1). Blood channels were not unusual and there was no fibrosis to suggest previous inflammatory changes.

Case 2. B. N., female, 10½ yr. of age. Developed swelling under R arm 3 wk. prior to surgical removal of this axillary mass. It was described as "peanut" in size, gradually enlarging to "egg" size with pain on palpation. There was no fever or other symptomatology. Definite history of cat scratch was obtained, approximately 2 to 3 wk. prior to onset.

Tuberculin Test (I.D.) 1:1000—negative. Chest RG—negative.

Antibodies to lygranum—positive (6 wk. after onset). Frei skin test—negative.

Cat scratch antigen—positive (1 cm. in diameter with wheal induration and redness).

Biopsy of axillary gland was performed after 3 wk. of illness.

Gross specimen consisted of a mass of axillary lymphatic tissue measuring 4 × 2.5 × 2 cm. Section of mass disclosed 3 discreet lymph nodes. They were light yellowish-tan in color and soft in consistency. Microscopically, 2 of the lymph nodes showed an atypical pattern while the third was completely normal in appearance. Two abnormal lymph nodes disclosed cortical and medullary architectural replacement by multiple large granulomatous foci (Fig. 2). These individual foci were com-

FIG. 2. Case 2. Necrotic polymorphonuclear leukocytes within center of one of granulomata. Capsular inflammatory change can be seen at R margin. ×55.

posed of aggregates of reticuloendothelial cells within center of which a broad zone of polymorphonuclear leukocytes could be identified. The latter cells showed evidence of pyknosis and karyorrhexis. A thin rim of lymphocytes in which blood vessels with hypertrophied endothelial cells were present surrounded these granulomata. Several subcapsular granulomata had extended into the capsule with discharge of this central necrotic material into adjacent fatty tissue. Capsule was enormously thickened and showed marked chronic inflammation and fat necrosis of perinodal adipose tissue.

Case 3. G. B., male, 4 yr. of age. History of cat scratch with small reddened papule on volar aspect of L wrist 3 wk. prior to onset of fever. At that time a mass in L axilla was noticed which was slightly tender. Fever subsided after 5 days but mass persisted and was removed surgically 3 wk. later.

Blood Examination: WBC count—7.8 thousand/cmm.; neutrophils, 36%; lymphocytes, 54%; monocytes, 4%; eosinphils, 6%; RBC count normal. Platelets normal.

Urinalysis—negative.

Tuberculin (O.T.) Test (I.D.)—1:1000—negative.

Antibodies to lygranum—negative (3 wk. from onset).

Frei skin test—negative.

Cat scratch antigen—position (2½ cm. × 2 cm. with wheal induration and redness).

Culture of gland—negative.

Biopsy of axillary gland was performed 5 wk. after onset of lymphadenopathy.

Gross specimen consisted of a mass of lymphatic tissue measuring 3 × 2 × 1 cm. and was soft and light cream-colored in appearance. Microscopically, this mass was found to be composed of 4 fused lymph nodes, all of which showed alterations in structure. Nodular capsules were thickened and a marked perivascular chronic inflammatory reaction was consistently present. Cortical zone was generally well preserved with lymph nodules showing marked germinal-center hyperplasia. The medulla, however, showed replacement of normal cords and sinuses by varying-sized epitheliod cell granulomata (Fig. 3). These latter cells, presumably of reticuloendothelial origin, were closely packed with no evidence of necrosis. Rare giant cells of the Langerhans type were noted. Fusion of adjacent granulomatous areas was common, with the result that large sheets of epithelioid cells were frequently observed.

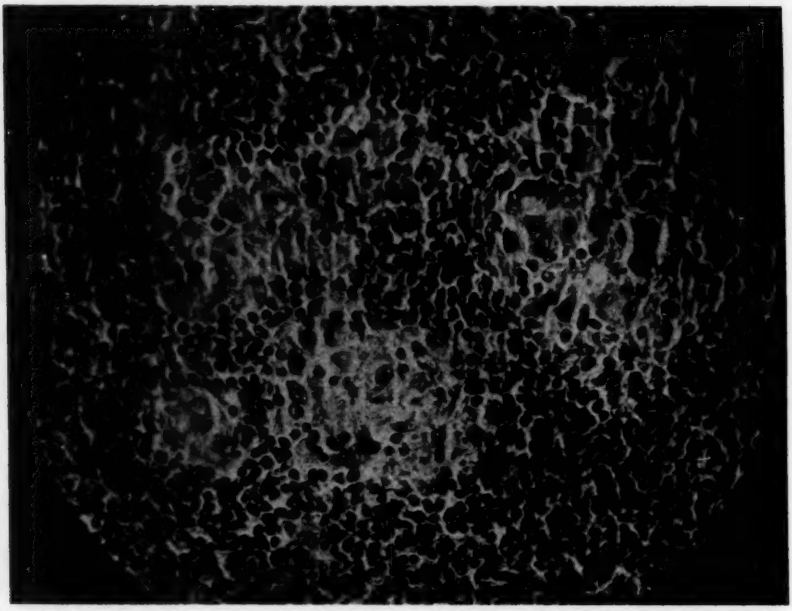

FIG. 3. Case 3. Several "epithelioid cell" granulomata showing tendency for coalescence of adjacent granulomata. ×450.

Case 4. M. K., female, 8 yr. of age. Swelling under R arm of 1 mo.' duration. It was about 2 cm. in diameter, firm, smooth and tender, increasing rapidly in size in last 2 wk. and associated with fever, listlessness and anorexia which lasted for several days. Patient was treated with penicillin, hot local packs, and local aspiration with little effect. Several scratch marks, presumably from the family cat, were noted on hands at time of onset of illness. Mass was excised approximately 5 wk. from onset.

Blood Examination: WBC count—13 thousand/cmm.; neutrophils, 60%; eosinophils, 10%; lymphocytes, 26%; monocytes, 4%; RBC count normal. Platelets normal.

Urinalysis—negative.

Tuberculin Test (I.D.)—1:1000—negative. Chest RG—negative. Trichinella skin test—negative.

Agglutinations—Brucella—negative. Paul-Bunnell—negative.

Stool examination for ova and parasites—negative.

Antibodies to lygranum—negative (6 wk. after onset). Frei skin test—negative.

Cat scratch antigen—(wheal, induration, and redness measuring 2 cm. in diameter—positive).

Culture of gland—negative.

Axillary lymphatic tissue received as 3 separate masses, largest measuring 3 × 2 cm. These were friable and soft in consistency. Microscopically, it is of considerable interest that only 1 of 3 masses of fused lymph nodes showed evidence of abnormal structure. Epithelioid cell granulomata in this mass of nodes were identical with those described in Case 3. There were, however, fewer granulomata and tendency of nearby lesions to fuse was not particularly prominent.

DISCUSSION

A review of the cases establishes certain criteria occurring constantly enough to be of diagnostic value. A history of contact and actual scratch by a cat was obtained in all instances. Of the cases seen early, each disclosed a peripheral skin lesion consisting of a healed papule with striking lack of lymphangitis but regional lymphadenopathy of variable

size. The site of lymph nodal enlargement was variable, the axillary region being most commonly affected since the hand was the most frequent site of injury, but inguinal, cervical, and nodes in the parotid area were also involved. Most of the nodes were tender on palpation and were described as being 3 to 4 cm. in diameter. Fever, so often emphasized as a clinical feature, was variable both as to its presence and also with respect to its duration and course. Case 1 illustrates the extreme prolongation of a septic type of fever which lasted approximately one month and was characterized by daily fluctuations of as much as 3° C. The pattern of this fever could well represent a variety of serious infections, but there was a striking contrast between the febrile curve and the clinical appearance of the patient. The only time prostration was evident was at the extreme peak of the fever. The pulse rate was proportionate to the degree of fever. In contradistinction to this, several patients (for example, Case 2) had no fever throughout the illness while the majority had moderate fever of only a few days' duration. Incubation period, as measured from the date of scratch to the onset of lymphadenopathy, was 2 to 3 weeks in all instances.

None of the patients have shown any sequelae following subsidence of their symptoms and signs and it is probable that the chemotherapeutic agents had little if any effect on the course, illustrated in Case 1.

Laboratory tests were helpful only in a negative sense and blood cell counts failed to show leukocytic response. Several showed an eosinophilia of 6 to 10% which may possibly have some clinical significance.

The inability to isolate and associate a specific etiologic agent with this clinical syndrome has unquestionably hampered investigation. The authors' studies, in agreement with other laboratories,[2] have resulted also in negative findings. Laboratory animals have been inoculated without success. Failure to isolate an agent emphasizes the need for further investigation. There are, however, several aspects of laboratory investigation that evoke discussion. The constantly negative Frei tests and positive complement-fixation (C.F.) tests (at least in some individuals)[3] with "Lygranum" suggests a unique relationship. A positive serologic reaction with the antigen of lymphogranuloma venereum (LG.V.) would indicate membership in the psittacosis-LG.V. group. Although most agents in this group can be readily isolated, failure to isolate an agent from this disease does not exclude association. It is known that at least two members of this group are resistant to isolation. The low incidence of positive reactions obtained by the C.F. tests would also tend to indicate that the antigen common to both agents is remote. Other investigators have also noted the low incidence of positive C.F. antibody.[2] Another consideration in regard to the serologic data is that the positive reactions may be nonspecific in nature and in no way associated with LG.V. Further emphasis regarding this "nonspecific" relationship can be inferred from the patient (Case 4) who yielded the skin-testing antigen. Repeated C.F. tests on sera from this individual were consistently negative. In Case 1 tests were positive over a period of several weeks and it is interesting to note that this individual alone demonstrated a chronic type of infection. Other serologic positive reactions remained so for short periods of time only.

A brief comment concerning the skin test is warranted inasmuch as this alone was positive in all these cases. The antigen was prepared in the manner described for the preparation of Frei antigen using purulent material obtained from one of the cases. All patients exhibited a wheal and area of erythema and induration within 48 hours and this persisted for several days. A control group of 10 "normal" individuals showed no skin

reaction. Cat scratch antigen and patients with LG.V. are too limited in amount or numbers to test the skin reaction on these individuals although a control group of such patients would be worthy of study. Nodes which have been removed from the cases have been frozen to be used for preparation of skin test antigen.

Instances of a positive skin sensitivity to the cat scratch antigen lasting over a period of years have been reported.[2] In view of this latter phenomenon this test becomes comparable with a tuberculin skin test and must be evaluated in terms of the clinical condition of the patient.

Although it must be emphasized that the diagnosis of cat scratch syndrome cannot be made with certainty from microscopic examination of the affected lymph nodes, certain histologic features are constant enough to be of at least suggestive evidence. All the cases studied microscopically, including children and adults, have shown a nonspecific epithelioid cell granulomatous type of inflammatory reaction. While these foci, which were both cortical and medullary in location, showed actual necrosis in nodes from children infrequently, necrotic polymorphonuclear leukocytes were consistently observed within the granulomata nodes from adults. Capsular fibrous tissue thickening with acute and chronic inflammatory changes was noted in nearly every case. Subcapsular necrotic granulomata sometimes extended through the capsule to produce fat necrosis of adjacent adipose tissue but cutaneous sinuses were not formed in any of these cases. In this connection it is pertinent that there seems to be no correlation between the degree of acute inflammation within the node and pericapsular tissue and the clinical status of the patient. This is illustrated in Case 2 in which, although the biopsy revealed minute abscesses throughout the nodes with extension into the perinodal adipose tissue, the patient was stated to be afebrile. In contradistinction, Case 1, which showed the least significant microscopic changes, had a septic type of fever curve for a period of one month. Another unusual pathologic characteristic of this syndrome is its tendency to affect groups of glands despite the fact that it is not unusual for a node with completely distorted architecture to lie adjacent to a normal node. The authors were impressed by the fact that within any given case all the microscopic lesions were at the same stage of development and saw no instances of the abscess type of lesion co-existing with the well preserved epithelioid cell type of pattern. The nonspecificity of this nodal histologic pattern readily accounts for the frequency with which the lesion has been confused with a variety of granulomatous inflammatory reactions including tuberculosis, tularemia, Boeck's sarcoid, brucellosis, lymphogranuloma venereum and even Hodgkin's disease.

Summary

The clinical, laboratory and pathologic findings of a series of cases of cat scratch syndrome have been reviewed. In spite of a variable clinical course, certain features associated with a selected group of laboratory tests appear to be constant enough to be of diagnostic value.

A history of contact with a cat and/or scratch which is usually associated with a peripheral skin lesion, lack of lymphangitis, presence of regional lymphadenopathy with tenderness to palpation are the most constant clinical findings. Fever, so frequently emphasized as a characteristic clinical sign, may be extremely variable in type and duration or entirely absent. A skin test with cat scratch antigen has been positive in all cases. Lacking this antigen, a negative Frei skin test in conjunction with a positive complement fixation test (Lygranum C. F.) is suggestive evidence for the diagnosis.

With positive evidence from the above data, biopsy of an affected gland with its relatively nonspecific pathologic picture is not considered essential for the establishment of the diagnosis of cat scratch syndrome.

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Spanish Abstract

Síndrome del rasguño de gato

La revisión clínica, de los examenes de laboratorio e histopatología de 15 casos de niños y adultos que han sido estudiados por los autores les hizo patente que a pesar de la variabilidad del cuadro, ciertas características clínicas asociadas con determinadas pruebas de laboratorio tengan valor diagnóstico por su presencia constante.

El cuadro clínico está ilustrado claramente, en uno de los casos estudiados, por su riqueza en síntomas. Se trataba de un niño de 4 años de edad que había sido rasguñado en la mano izquierda por un gato—sitio en el cual le apareció una pústula subsecuentemente—tres semanas antes de que se iniciara fiebre diaria hasta de 105° que no respondió a la cloromicetina, aureomicina ni penicilina, persistiendo por mas de 15 dias. Al examinarlo se le encontró un ganglio linfático de la axila izquierda infartado como de 3 cm. de diámetro y algo doloroso a la palpación, tenía además una pápula cicatricial en la cara dorsal de la mano izquierda, y ligera congestión faríngea y de la úvula. El estudio histopatológico del ganglio reveló principalmente una reacción granulomatosa inespecífica formada por la acumulación aparentemente de células reticuloendoteliales.

La revisión de los pacientes demostró que todos tenían historia de contacto o rasguño de gato y en los enfermos examinados en su principio la lesión periférica consistía de una papula curada con sorprendente ausencia de linfangitis pero con linfadenopatía de tamaño variable, mas frecuentemente axilar por ser la mano el sitio a menudo lesionado, pero también fueron afectados los ganglios inguinales, cervicales y los de la región parotidea. Generalmente eran dolorosos y alcanzaban un diámetro hasta de 3 y 4 cm. La fiebre fué extremadamente variable desde una curva térmica de tipo séptico de un mes de duración, con fluctuaciones de varios grados, hasta la ausencia completa, pero generalmente la presentaron en forma moderada. Es interesante señalar, que aun cuando fuera intensa no producía una postración evidente sino cuando llegaba a su altura máxima contrariamente a otras curvas conocidas de tipo séptico.

El periodo de incubación medido desde el momento del rasguño hasta el principio de la adenopatía fue invariablemente de 2 a 3 semanas. Ninguno de los enfermos respondió a los antibióticos y tampoco quedó secuela alguna al hacerse la remisión de los síntomas y signos. Los exámenes de laboratorio de rutina solo tuvieron valor por ser negativos, no hubo leucocitosis franca pero algunos enfermos presentaron eosinofilia de 6-10% que pudiera tener cierta significación.

Aunque no ha sido posible aislar un agente etiológico específico y los animales comunes de laboratorio no han podido inocularse con éxito los autores encontraron que la cutirreacción de Frei fué siempre negativa pero las pruebas de fijación del complemento con el antígeno del linfogranuloma venereo, aunque en escasa incidencia, eran positivas. Aunque este hecho es de posible significación en cuanto a que se trate de un organismo del grupo psitacosis-linfogranuloma venereo, no obstante que estos gérmenes han sido fácilmente aislados, podría simplemente explicarse como una reacción inespecífica y no de grupo, máxime que en el enfermo del cual se obtuvo material para hacer el antígeno para cutirreacciones las reacciones del complemento en su suero fueron repetidamente negativas. Cualquiera que sea la significación de la reacción de fijación del complemento con el antígeno del linfogranuloma venereo, si esta es positiva y la reacción de Frei es negativa, y con mas razón, si la cutirreacción con

antígeno obtenido de la pústula producida por el rasguño del gato es positiva, la evidencia es sugestivamente diagnóstica. Esta última reacción se encontró positiva en todos los enfermos a las 48 horas y persistió por varios días teniendo aun mayor significación por haber sido controlada en 10 individuos aparentemente normales en los cuales fue negativa. En vista de que se han señalado casos en que la reacción persiste por varios años, debe interpretarse de acuerdo con las manifestaciones clínicas del enfermo en forma semejante a las de la prueba cutánea de la tuberculina.

Aunque la biopsia del ganglio no es diagnóstica por si misma en forma definitiva, las siguientes características, son cuando menos sugestivas: reacción inflamatoria de tipo granulomatoso de células epitelioides, frecuencia de necrosis de estos focos, ya de localización cortical o medular, en el adulto, y raramente en el niño; engrosamiento fibroso frecuente de la cápsula con cambios inflamatorios agudos y crónicos, necrosis del tejido adiposo subyacente por diseminación del proceso necrótico subcapsular a traves de la cápsula, pero sin formación de fistulas cutáneas, ausencia de correlación entre el grado de inflamación aguda del ganglio y tejido periganglionar y la intensidad de la fiebre; tendencia a afectar grupos de ganglios a pesar de que no es raro que un ganglio linfático con lesiones marcadas yasga adyacente a uno normal y finalmente la coexistencia de las lesiones en el mismo estadío de desarrollo. Esta inespecificidad relativa de las características histopatológicas que ha ocasionado su confusión con las de la tuberculosis, tularemia, sarcoide de Boeck, brucelosis, linfogranuloma y aun con la enfermedad de Hodgkin, no son esenciales para el diagnóstico si el cuadro clínico y las reacciones cutáneas con antígeno de rasguño de gato y de fijación del complemento con el antígeno de la linfogranulomatosis venérea son positivas y la reacción de Frei es negativa.

766 Irving Avenue

STUDIES IN PANCREATIC FIBROSIS

Cor Pulmonale: Clinical and Pathologic Observations

By ALEXANDER S. NADAS, M.D., GILBERT COGAN, M.D., BENJAMIN H. LANDING, M.D., AND HARRY SHWACHMAN, M.D.

Boston

COR PULMONALE, pulmonary heart disease, is a syndrome encompassing the effects of primary lung disease on the circulation. Acute cor pulmonale resulting from extensive pulmonary embolism demonstrates in simple fashion the effects on the heart of a sudden obstruction of the pulmonary vascular tree.[1] Chronic cor pulmonale, resulting from a variety of causes, i.e., emphysema, chronic lung infection, asthma, silicosis, kyphoscoliosis, is the outcome of a number of complicated physiologic processes among which gradual increase in pulmonary arterial pressure, anoxia, hypervolemia and polycythemia may be mentioned.[2] The majority of publications relating to cor pulmonale emphasize the occurrence of this syndrome in older age groups.[3-6] Within the past five years, however, two publications have focussed attention on the occurrence of chronic cor pulmonale in the pediatric age group, particularly in infants and children with pancreatic fibrosis.[7, 8]

An awareness of the problem of cor pulmonale in pancreatic fibrosis has existed for many years. In view of the recent interest in this problem, it seemed timely to summarize the authors' experience with the cardiac complications of this disease. The purpose was to determine the frequency and significance of pulmonary heart disease in patients with pancreatic fibrosis. Accordingly a study has been made of a number of patients followed regularly by the authors and much of the available pathologic material has been reviewed.

MATERIAL AND METHODS OF INVESTIGATION

The 46 cases forming the basis of the clinical part of this study have been selected from the total current group of about 150 patients with pancreatic fibrosis on the basis of severity alone. Only those patients were included who had severe pulmonary disease as demonstrated by physical examination and roentgenogram and who were limited in their activities. They were found to be retarded physically and all were at the 25th percentile or below when their weights and heights were plotted on developmental charts.[9] No patient in this group showed evidence of intrinsic heart disease. All were studied by means of detailed history, physical examination by one or more persons, roentgen examination of heart and lungs, electrocardiography using both standard and unipolar leads, and all routine and special laboratory technics necessary to establish the diagnosis of pancreatic fibrosis.[10] Clinical criteria for cor pulmonale included the presence of cardiac enlargement by physical examination (considered least reliable) or by RG, electrocardiographic evidence of R ventricular hypertrophy,[11, 12] or clinical evidence of systemic congestion (i.e., distended neck veins, hepatomegaly of over 3 cm., edema or anasarca).

Pathologic material was obtained by studying detailed protocols of patients with pancreatic fibrosis (35 in number) who were autopsied at the Children's Medical Center between 1944 and 1949. In order to evaluate the significance of pathologic findings, a comparative study was made of a control group of autopsy protocols of patients of same age range who died during the same period of time as the pancreatic fibrosis patients. In selecting these controls (25 in number), patients with chronic

From the Division of Laboratories and Research of the Children's Medical Center, and from the Departments of Pediatrics and Pathology, Harvard Medical School, Boston.

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pulmonary disease, renal disease, anemia and primary and secondary heart disease were excluded. A comparison of heart weight and relative thickness of R and L ventricles was made. The presence or absence of congestive failure was judged on the basis of evidence of passive congestion in liver and other abdominal organs.

Results

A. Pathologic: Table 1 summarizes the postmortem data for the patients with pancreatic fibrosis and the control patients; for purposes of differentiating the physiologic right ventricular hypertrophy of the neonatal period from that produced by the disease processes in pancreatic fibrosis, separate values for patients under and over 6 months of

TABLE 1

Postmortem Data

Thickness R Ventricle / Thickness L Ventricle	Patients	Controls
Total	.48	.37
under 6 mo.	.51	.34
over 6 mo.	.47	.40
Average Ratio of Cardiac Weight to Normal		
Total	1.17	1.17
under 6 mo.	0.99	1.28
over 6 mo.	1.34	1.08
(Cardiac Weight/Body Weight)×100		
Total	.81	.63
under 6 mo.	.76	.65
over 6 mo.	.88	.62
Average Ratio of Body Weight to Normal		
Total	.69	.87
under 6 mo.	.64	.93
over 6 mo.	.76	.82
Average Ratio of Renal Weight to Normal		
Total	.99	1.04
under 6 mo.	.92	1.00
over 6 mo.	1.06	1.07

age are included. As can be seen, patients with pancreatic fibrosis in both age groups showed greater relative thickness of the right ventricle than did the controls. Although the average cardiac weights of patients with pancreatic fibrosis, in terms of normal standards by age,* were the same as those of the controls, the average heart weight as a percentage of body weight was higher in the patients with pancreatic fibrosis in both age groups. This suggests that there is a definite tendency to cardiac enlargement in this disease, which is partially masked by the effect of malnutrition, most markedly so in the younger patients. As the table shows, the body weights of patients with pancreatic fibrosis were significantly lower than those of the controls, especially in the group dying under 6 months of age. The values for the kidneys were included for comparison, since their weight remains relatively stable under varying states of nutrition. This is confirmed by the data, the renal weights in the patients with pancreatic fibrosis, and in the controls not differing significantly from normal values.

* Normal values taken from tables of Coppoletta and Wolbach[13] and Holt and McIntosh.[14]

TABLE 2

THICKNESS R VENTRICLE: POSTMORTEM DATA

Thickness	No. of Cases	
	Patients (35) %	Controls (25) %
.10 to .19 cm.	3	0
.20 to .29 cm.	20	40
.30 to .39 cm.	37	28
.40 to .49 cm.	17	24
.50 to .59 cm.	20	4
.60 to .69 cm.	3	4

Table 2 lists the incidence of right ventricular thickening in the two groups of patients. It would appear from this data that no absolute value for right ventricular thickness can be considered diagnostic of right ventricular hypertrophy.

In the group of 35 autopsied patients with pancreatic fibrosis, there were only two with pathologic evidence of right-sided congestive failure. The other 33 patients died with evidence of infection and overwhelming pulmonary disease.

B. Clinical: Utilizing the criteria for cor pulmonale as outlined under Methods, the clinical material was divided into two groups. Table 3 summarizes the pertinent findings in the patients with clinical cor pulmonale. Table 4 presents the findings in those patients whose pulmonary disease did not demonstrably affect the heart. From this latter table, the data relative to cardiac status were omitted since, by definition, they were all negative.

It may be seen from tables 3 and 4 that out of a total of 46 patients, 8 (17.4%) had some clinical evidence of cor pulmonale.

Sex: There were 5 females and 3 males among the patients with cor pulmonale and 20 females and 18 males without cor pulmonale.

Age and Pulmonary Symptomatology: Average age of the patients with cor pulmonale at the time of evaluation was 3 3/12 years with a minimum of 1 1/12 and a maximum of 6 4/12. The average age of the patients without cor pulmonale was 6 6/12 with a minimum of 6/12 and a maximum of 17 years. Comparing the age of onset of pulmonary

TABLE 3

PATIENTS WITH COR PULMONALE

Patient	Age (yr.) at Evaluation	Duration (yr.) of Pulmonary Symptoms		Severity of Pulmonary Signs and Symptoms				Cardiac Status			Nutritional Status Percentile		Outcome
		Prior to Therapy	With Therapy	RG	Dyspnea	Clubbing	Cyanosis	Enlargement	Systemic Manifest.	ECG	Wt.	Ht.	
1. J.N.	6 4/12		6	++	+	+	0	0	0	+	3	3	Alive
2. K.R.	5 8/12	3	1	++	+	+	+	0	+	0	<3	<3	Alive
3. P.W.	4 2/12	1½	2½	++	+	+	+	0	+	0	<3	<3	Died
4. C.W.	2 3/12		2 1/12	++	+	0	+	0	0	+	<3	<3	Alive
5. O.C.	2 2/12	1	1	++	+	+	+	+	+	+	<3	<3	Died
6. B.S.	2 4/12	10/12	1	++	+	+	+	0	0	+	<3	<3	Alive
7. L.K.	2 6/12		1 9/12	++	+	+	+	+	0	+	10	3	Alive
8. R.E.	1 1/12	1 1/12		++	+	0	0	0	0	+	10	10	Alive

TABLE 4

Patient		Age (Yr.) at Evaluation	Duration (Yr.) of Pulmonary Symptoms		Severity of Pulmonary Signs and Symptoms				Nutritional Status Percentile		Outcome
			Prior to Therapy	with Therapy	RG	Dyspnea	Clubbing	Cyanosis	Wt.	Ht.	
1.	A.S.	17	14	1	+	−	−	−	25	25	
2.	V.D.	12	11	0	+	−	−	−	10	10	
3.	B.H.	11	2	9	++	+	+	+	<3	3	
4.	E.E.	12	7	3	++	−	+	−	<3	<3	
5.	J.D.	9 9/12	9	None	++	−	+	−	25	10	Died
6.	D.F.	12 1/12	6	3	+	−	+	−	<3	3	
7.	P.R.	10	5 9/12	3	+	−	−	−	25	25	
8.	B.Y.	8 8/12	4 8/12	4	++	−	+	−	<3	<3	
9.	H.T.	8 6/12	2½	6	++	−	−	−	<3	<3	
10.	L.D.	8 2/12	8 2/12	0	++	−	+	−	25	25	
11.	C.P.	8 1/12	6 1/12	2	++	+	+	−	3	<3	
12.	S.H.	8 4/12	6 10/12	1 2/12	++	−	+	+	<3	<3	
13.	J.F.	12 2/12	2½	5	++	−	+	−	<3	10	
14.	M.B.	7½	3	4	++	+	+	−	<3	<3	Died
15.	F.B.	7 10/12	9/12	6 3/12	+	−	−	−	25	10	
16.	R.C.	6 10/12	3 6/12	3	++	−	+	−	<3	10	
17.	E.G.	6 2/12	5 2/12	1	++	−	+	−	<3	10	
18.	R.K.	6	5	1	++	+	+	−	<3	<3	
19.	D.S.	6 2/12	2 6/12	3	++	−	+	+	<3	<3	
20.	J.P.	6 6/12	5 5/12	None	++	−	+	−	<3	10	
21.	D.C.	5	2 10/12	2 2/12	+	+	+	−	<3	<3	
22.	N.B.	4 8/12	7/12	4 1/12	++	+	+	+	<3	<3	Died
23.	K.G.	4 2/12	3 2/12	1	+	−	−	−	<3	<3	
24.	R.C.	3 11/12	10/12	3	++	+	0	+	<3	<3	
25.	E.B.	4	3	8/12	++	+	+	−	<3	<3	Died
26.	R.D.	4 2/12	8/12	3 8/12	++	+	+	−	<3	<3	
27.	J.W.	3 6/12	6/12	3	++	+	+	+	10	10	
28.	J.M.	3 10/12	1/12	3 4/12	++	+	+	+	<3	<3	
29.	P.G.	3 2/12	2 9/12	3/12	+	+	−	−	<3	<3	
30.	N.T.	4	6/12	2	+	+	+	−	3	<3	
31.	W.S.	9	1 6/12	1	++	+	+	−	3	<3	
32.	P.F.	2 10/12	2/12	2½	++	+	+	−	<3	<3	
33.	J.S.	2 4/12	2 4/12	0	+	+	+	−	<3	<3	
34.	R.G.	6	2	0	+	−	−	−	25	10	Died
35.	R.F.	2	1 3/12	0	+	−	−	−	<3	<3	
36.	P.F.	1 3/12	1 2/12	0	++	+	−	−	<3	<3	
37.	C.K.	1	6/12	6/12	+	+	−	−	<3	<3	
38.	A.S.	6/12	6/12	0	++	+	+	−	<3	<3	

symptoms in the two groups, we find that each one of the eight patients with cor pulmonale started to show respiratory symptoms before 6 months of age, whereas only 15 (39%) of the 38 patients without cor pulmonale developed their pulmonary symptoms at 6 months of age or less.

In 5 of the 8 patients with cor pulmonale and 29 of the 38 patients without cor pulmonale, there was a lapse of one year or more between the onset of the pulmonary symptoms and the beginning of antibiotic therapy.[15]

Comparing the severity of the pulmonary symptoms in the two groups, one is impressed

by the fact that all the patients with cor pulmonale had noticeable dyspnea and extensive pulmonary involvement by roentgen examination. All but one member of this group showed digital clubbing and/or cyanosis. In contrast to this, 14 patients without pulmonary heart disease had only moderate degree of pulmonary change by chest roentgenogram and exactly half of them were without obvious dyspnea. Slightly less than one third of them (12 patients) had neither clubbing nor cyanosis.

Cardiac Status: Analyzing the cardiac status of the patients, it became evident that the diagnosis of cor pulmonale is most readily made by electrocardiography. Three patients with electrocardiographic patterns indicating significant right ventricular hypertrophy also showed cardiomegaly. Two more patients showed right ventricular hypertrophy by electrocardiogram without any other evidences of pulmonary heart disease. Two patients with peripheral edema and significant hepatomegaly failed to show either an enlarged heart or right ventricular hypertrophy by electrocardiogram.

Nutrition: The relatively poor nutritional state of the patients included in this study should be pointed out. No patient was above the twenty-fifth percentile line in weight or height. Even within these relatively poorly nourished groups, however, certain differences could be observed. There was no patient with cor pulmonale whose nutritional state placed him above the tenth percentile line of the growth charts, whereas slightly less than a third[12] of the children without cor pulmonale were above it.

Prognosis: At present, 2 of the 8 patients with cor pulmonale and 5 of the 38 patients without cor pulmonale have died. Hence, the clinical evidence of pulmonary heart disease does not necessarily mean an immediately poor prognosis.

Discussion

The concept of chronic cor pulmonale may be approached from the physiologic, pathologic and clinical view points.

The physiologist regards the presence of pulmonary arterial hypertension, i.e., mean pulmonary artery pressures of 25 mm.Hg or more, as the essential factor in cor pulmonale. Mild degrees of this condition (pulmonary arterial hypertension uncomplicated) can only be discovered by means of right heart catheterization. More severe degrees are revealed by the presence of cardiac enlargement or by electrocardiograms of the right ventricular hypertrophy pattern. This stage may well be called cor pulmonale, compensated. The final stage of the disease is cor pulmonale in failure, i.e., when signs and symptoms of peripheral edema and congestion are added to the picture of pulmonary disease and right ventricular hypertrophy.

Without discussing elaborately the etiology of pulmonary arterial hypertension, hypoxia, resulting from emphysema, is the most important contributing factor, beside which anatomic alterations of the pulmonary vascular bed and hypervolemia take secondary places.[16]

The authors have not as yet catheterization data on the patients with pancreatic fibrosis. However, in view of the severe degree of emphysema and atelectasis, due to bronchial plugging, combined with the chronic staphylococcal pneumonia, that is an integral part of the severe form of this disease, it seems very likely that a significant degree of pulmonary hypertension exists.

The pathologist defines cor pulmonale in terms of right ventricular enlargement or visceral congestion and edema. The presence of right ventricular enlargement, pathologically, is easily detected in severe cases where the total weight of the heart and the thickness of the right ventricular wall are significantly increased. The existence of cor pulmonale of

lesser severity is more difficult to demonstrate. The total cardiac weight is usually not increased in these cases, and the estimation of ventricular wall thickness depends to such a great extent on the technic by which the measurement is performed that the significance of minor differences (1-2 mm.) is hard to evaluate.

In this series of autopsies, the average absolute cardiac weights of the total control group and the total group with pancreatic fibrosis, in terms of normal cardiac weights, were the same, although the patients with pancreatic fibrosis showed a definite increase in absolute cardiac weight with age, in contrast to the control series. At all ages, the patients with pancreatic fibrosis had a greater cardiac weight, relative to body weight, than the controls. More patients with pancreatic fibrosis showed right ventricular thickness of 0.5 cm. or more than did the normals, but 8% of the latter group still showed what by conventional criteria would be considered right ventricular hypertrophy. The average ratio of right ventricular to left ventricular thickness was appreciably higher in the pancreatic fibrosis group than in the controls. This ratio may be a more reliable index of right ventricular hypertrophy than either absolute cardiac weight or absolute right ventricular thickness.

Since in only 2 of the 35 patients with pancreatic fibrosis were the visceral findings suggestive of frank right ventricular failure, the pathologic studies support the clinical conclusion that decompensated cor pulmonale is rare in patients with pancreatic fibrosis. It is possible that differences in the pathologic criteria of cor pulmonale account for a discrepancy with some other reports in this regard.

To the clinician, cor pulmonale reveals itself either by cardiomegaly or right ventricular hypertrophy (cor pulmonale, compensated) or by signs of right ventricular failure (cor pulmonale, decompensated). Though the electrocardiogram may well be the most sensitive means for the discovery of right ventricular hypertrophy, recent evidence points to the fact that only at right ventricular pressures of 30 mm.Hg or more do the tracings begin to show definite signs of right ventricular hypertrophy.[17]

The data presented reveal that only a minority (17%) of the patients with severe pancreatic fibrosis showed clinical evidences of pulmonary heart disease. On the average, the patients with cor pulmonale were younger, the onset of their pulmonary symptoms occurred at an earlier age, they were more undernourished, and they all had severe pulmonary symptoms and signs, including digital clubbing or cyanosis.

The authors also found, in agreement with others, that cardiomegaly was rare and that the electrocardiogram seemed to be the most sensitive clinical tool for demonstrating the presence of pulmonary heart disease. It could not be substantiated that the contention that cor pulmonale with failure is a frequent cause of death in patients with pancreatic fibrosis. Only 2 of the 46 patients studied clinically went into frank right-sided failure and only one of these died. The other recovered after appropriate treatment was instituted.

Although seemingly many of the conditions predisposing to the development of pulmonary arterial hypertension are present in pancreatic fibrosis, clearcut clinical evidence of cor pulmonale could be found only in a minority of the patients studied. This does not preclude the assumption that pulmonary arterial hypertension demonstrable only by right-heart catheterization may well have been present in a sizeable proportion of the same patients.

A comparison of the effects of systemic arterial hypertension on the left ventricle with those of pulmonary arterial hypertension on the right ventricle may explain the paucity of clinical and autopsy findings in these patients. It is well known that systemic arterial

hypertension of considerable degree may exist for many years before its effect on the left ventricle can be demonstrated. In the same fashion, the authors believe that significant degrees of pulmonary arterial hypertension may well be present for some time before the development of real cor pulmonale. This assumption is supported by physiologic and pathologic data in the literature, emphasizing the long duration of pulmonary symptoms necessary for the development of clinically and pathologically demonstrable pulmonary heart disease.

It seems quite possible that with increased efficiency of antibiotic treatment, the life expectancy of patients with pancreatic fibrosis will increase and pulmonary heart disease may become more of a problem. For the present, however, pulmonary infection seems still the major threat to the life of patients with pancreatic fibrosis.

Summary

1. The cardiac complications of pancreatic fibrosis were studied by clinical examination and autopsy.

2. Of 45 patients with severe pancreatic fibrosis studied clinically, 8 showed cor pulmonale. One of these eight died in right-heart failure, the others showed only electrocardiographic changes characteristic of right ventricular hypertrophy.

3. A comparison of the autopsy findings of 35 patients with pancreatic fibrosis with those of a control series showed no diagnostic differences in cardiac weight or absolute right ventricular thickness. The ratio of right to left ventricular thickness, however, was higher in the group with pancreatic fibrosis, as was the ratio of cardiac weight to body weight. Only 2 out of 35 autopsies showed visceral edema and congestion of significant degree, suggestive of frank right ventricular failure.

4. Physiologic and pathologic considerations are presented concerning the development of pure pulmonary hypertension and its relationship to cor pulmonale, compensated or decompensated.

5. The data presented here suggest that the pulmonary involvement associated with infection is still the principal threat to life in patients with pancreatic fibrosis and the one towards which major therapeutic efforts should be directed.

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SPANISH ABSTRACT

Estudios en Fibrosis Pancreática; Observaciones Clínicas e Histopatológicas sobre Cor Pulmonale

En vista del interes reciente acerca del cor pulmonale en la fibrosis pancreática los autores resumen su experiencia, en este artículo, acerca de su frecuencia y significación.

El material estudiado lo forman 45 enfermos con fibrosis pancreática severa de los cuales solo 8 presentaron cor pulmonale. La edad promedio de los enfermos afectados fué de 3 3/12 años, los síntomas respiratorios del cuadro de fibrosis se iniciaron, en los 8 casos, antes de los 6 meses de edad y en el grupo control solo en el 39% comenzaron en esa edad o antes. La severidad clínica en el grupo con cor pulmonale fué impresionante; todos tenían disnea apreciable y lesiones pulmonares muy extensas en las placas de rayos X. Con excepción de un caso todos presentaron dedos en palillo de tambor y cianosis o cuando menos cianosis exclusivamente. En el grupo control algo mas de ⅓ parte de ellos solo tenían lesiones pulmonares moderadas, la mitad no presentaban disnea y menos de la tercera parte no tenían ni dedos hipocráticos ni cianosis. En el momento actual han muerto 2 de los casos con cor pulmonale y 5 de los enfermos sin dicha complicación por consiguiente se puede decir que esta no significa, necesariamente, mal pronóstico inmediato. Uno de ellos murió en insuficiencia cardiaca derecha y los restantes solo mostraron cambios electrocardiográficos característicos de hipertrofia ventricular derecha.

La comparación de los datos de autopsia de 35 casos de fibrosis pancreática, con los de una serie control no demostró diferencia diagnóstica en el peso del corazón o el grosor absoluto del ventrículo derecho, sin embargo, el grosor de las paredes del ventrículo derecho fué mayor que las del izquierdo en el grupo con fibrosis pancreática e igual pasó con la relación entre el peso del corazón y el peso corporal. Solamente 2 de estos 35 casos autopsiados mostraron edema y congestión visceral en grado significativo sugiriendo una insuficiencia ventricular derecha franca.

El concepto del cor pulmonale crónico puede considerarse desde el punto de vista fisiológico, histopatológico y clínico. El fisiólogo considera la presencia de hipertensión arterial pulmonar, por ejemplo, de 25 mm. de Hg como promedio, de presión en la arteria pulmonar o más, como un factor esencial en el cor pulmonale. Los grados moderados (hipertensión arterial pulmonar no complicada) solo pueden ser descubiertos por medio de cateterismo del corazón derecho y los grados mas intensos se revelan por la presencia de hipertrofia cardiaca o por electrocardiogramas con patrones de hipertrofia ventricular derecha, que bien pueden llamarse estadío de cor pulmonale compensado.

El estadío final de la enfermedad es el cor pulmonale en insuficiencia cuando los signos y síntomas de edema y congestión periférica se añaden al cuadro de la enfermedad pulmonar e hipertrofia ventricular derecha.

Aún cuando los autores no tienen todavía datos algunos de cateterismo en sus enfermos de fibrosis pancreática, en vista de los grados severos de enfisema y atelectasia debidos al taponamiento bronquial, combinado con la neumonía estafilocócica crónica que es parte integral de las formas severas de esta enfermedad, parece ser muy probable que exista cierta hipertensión pulmonar de significación.

Desde el punto de vista del patólogo se define el cor pulmonar en terminos de hipertrofia ventricular derecha o congestión visceral y edema.

En los casos severos la hipertrofia es facil de determinar cuando tanto el peso del corazón como el grosor de la pared ventricular derecha estan aumentados francamente, pero no así en los casos menos intensos en que el peso no está aumentado y el grueso de la pared depende en gran parte de la técnica con que se mida y la significación de diferencias ligeras (de 1-2 mm.) son difíciles de evaluar.

Para el clínico el cor pulmonale se revela por si mismo ya sea por cardiomegalia o hipertrofia ventricular derecha (cor pulmonale compensado) o por signos de insuficiencia ventricular derecha (cor pulmonale descompensado). Aunque el electrocardiograma pueda muy bien ser el medio mas sensible para descubrir la hipertrofia ventricular derecha pruebas recientes señalan el hecho de que solo cuando la presión en el ventrículo derecho es de 30 mm. de mercurio o más, los trazos empiezan a mostrar signos definitivos de hipertrofia ventricular derecha.

Los autores concluyen que aunque muchas de las condiciones que predisponen al desarrollo de hipertensión arterial pulmonar están presentes en la fibrosis pancreática, pruebas clínicas claras de cor pulmonale solo pudieron encontrarse en la minoría de los pacientes estudiados, aunque este hecho no invalida la posibilidad de que en una buena proporción de ellos esté presente la hipertensión de la arteria pulmonar que solo sería demostrable con el cateterismo derecho del corazón. Por otra parte, es lógico asumir que es necesaria la persistencia por largo tiempo de los síntomas pulmonares para que se desarrolle clínica e histopatológicamente el cuadro de cor pulmonale análogamente al mecanismo de sufrimiento del ventrículo izquierdo cuando existe hipertensión arterial sistémica.

Es posible que con la eficacia creciente de la terapéutica antibiótica aumente la sobrevida de los enfermos con fibrosis pancreática y el cor pulmonale llegue a ser un problema, pero actualmente la lesión e infección pulmonar de estos enfermos sigue siendo la amenaza principal de su vida y hacia ella deben dirigirse los esfuerzos terapéuticos mas grandes.

300 Longwood Avenue

STUDIES OF THE IMMUNOLOGY OF THE NEWBORN INFANT

II. Interference with Active Immunization by Passive Transplacental Circulating Antibody

By JOHN J. OSBORN, M.D.,* JOSEPH DANCIS, M.D., AND JUAN F. JULIA, M.D.
New York City

THIS study was designed to obtain quantitative data on the effect of passive transplacental circulating antibody on the active immunization of the very young infant.

The infant at birth is known to have circulating antibodies of many kinds which he has derived from his mother by passage through the placenta.[1-6] These antibodies gradually disappear during the first few months of life and are usually not measurable after about 6 months of age. As far as is known, they represent passive immunity only. Their presence in high concentration during the first few months of life has been shown capable of interfering with active immunization.[7-9]

In an attempt to define more closely the quantitative aspects of this interference phenomenon, the authors have studied it in relation to a single antigen-antibody system: diphtheria. In part I of this study,[10] infants of various ages who had no circulating diphtheria antitoxin were immunized with a single injection of a special high titer diphtheria toxoid (alum-adsorbed) and the antitoxin response followed at intervals afterwards for several months. The advantages of this technic for quantitative study were presented. This material provided normal controls for the present study in which the identical technic and toxoid were used, but on infants with measurable circulating antibody derived transplacentally from the mother.

MATERIALS AND METHODS

This work was made possible by the cooperation of the New York Foundling Hospital. Materials and methods were identical with those used in Part I of this study.[10]

A single dose of a diphtheria toxoid adsorbed on alum, 100Lf in 0.5 cc., was injected in the deltoid region of the infant. Blood specimens were obtained for measurement of antitoxin response at regular intervals up to 6 mo. after immunization. This study is concerned only with infants who were found to have circulating diphtheria antitoxin in the blood specimen taken at the time of immunization.

None of the infants had been previously immunized, therefore the circulating antitoxin found in the first blood specimen was assumed to represent transplacental maternal antitoxin. When possible, maternal blood was also drawn and the antitoxin content measured. In all cases the maternal titer was within the expected range calculated from the infant's titer by an adaptation of the formula of Barr and Glenny.[6] No mothers were immunized with diphtheria toxoid during pregnancy. Their circulating antibody presumably represented response to previous immunizations or contact with the disease.

From the Department of Pediatrics, New York University College of Medicine, and New York Foundling Hospital, New York City.

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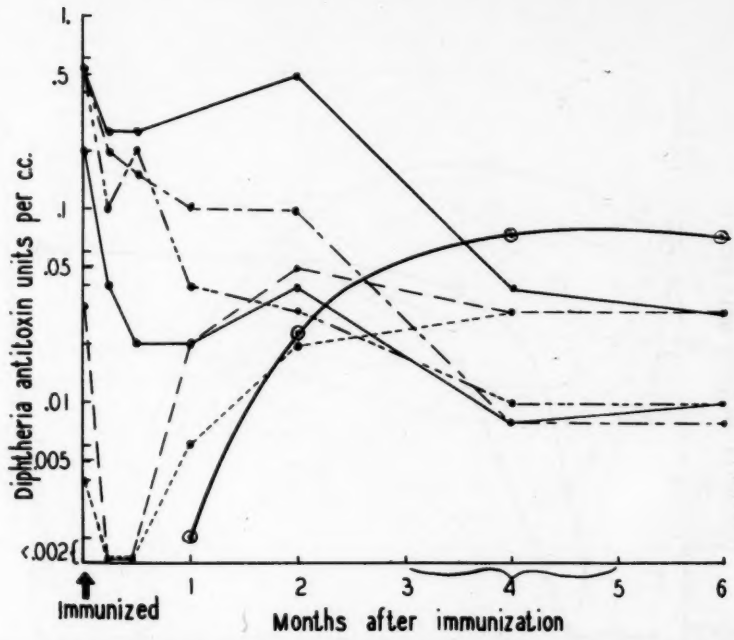

CHART 1. Response to immunization of 6 infants under 2 wk. of age who carried passive (transplacental) antitoxin, compared with normal mean response (ringed-dot curve) of infants without passive antitoxin.

Antibody titer on this and subsequent curves is represented on logarithmic scale.

RESULTS

In all, 23 infants ranging in age from under 2 weeks old to almost 6 months old were immunized. Diphtheria antitoxin levels at the time of immunization ranged from .003 units/cc. serum to 0.5 units.

Because there is a strong age differential in the antitoxin response to diphtheria toxoid,[10] the infants were divided into three groups according to the age at which they were immunized. There were 6 infants immunized when under 2 weeks of age, 8 infants at one month of age and 9 infants between 2 and 6 months of age.

The antitoxin responses of these three groups of infants are shown in charts 1, 2 and 3. Because there is so much variability in response, the curve of response for each separate infant immunized is shown. On the same chart, the mean response of normal infants without circulating antitoxin is shown for purposes of comparison. Each curve begins with the serum antitoxin level of the infant at the time of immunization (which represents entirely passive, maternal antitoxin).

Detailed data for the infants followed is given in table 1. The variation in the data is large, compared to the number of cases in each group. Statistical analysis of this data would have been more elaborate than the material would justify whereas restricted but useful conclusions can be drawn from simple inspection of the data.

In chart 1, representing the response of infants less than two weeks old at immuniza-

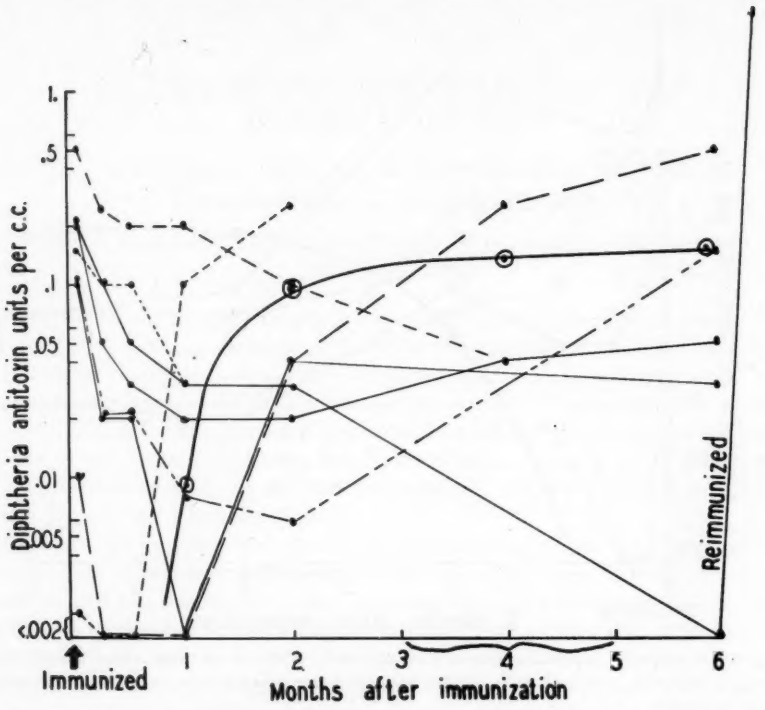

CHART 2. Response to immunization of 8 infants 1 mo. old who carried passive (transplacental) antitoxin, compared with normal mean response (ringed-dot curve) of infants without passive antitoxin.

tion, the two infants with the lowest antitoxin titers at time of immunization (.004 and .03 u./cc. serum) appear to respond almost normally with antitoxin production. However, the four infants immunized when they had circulating antitoxin titers of over 0.1 unit/cc. serum clearly do not respond with the normal production of antitoxin.

In chart 2, representing the response of infants one month old at immunization, the difference in response of infants with low and with high antitoxin titers is even more striking. The two infants with initial levels of .01 and .002 u./cc. respond well. But the six infants with initial titers of 0.1 and above respond poorly. One infant does not show any measurable antitoxin six months later (less than .002 u./cc.).

Again in chart 3 (infants 2 months older and over) the 7 infants with initial titers of .04 and below are close to normal in response, but the 2 infants with levels of 0.1 and 0.15 do not form a normal amount of antitoxin.

From this data, it is not possible to pick an exact antitoxin level at which interference with active immunization will take place. Vahlquist, using a less potent diphtheria toxoid on alum as antigen (40 Lf), found that a level of circulating antitoxin of approximately .02 u./cc. was the critical level for interference with immunization. The present authors' data would seem to indicate a slightly higher critical titer, near 0.1 u./cc. This is probably because of the greater potency of the antigen.

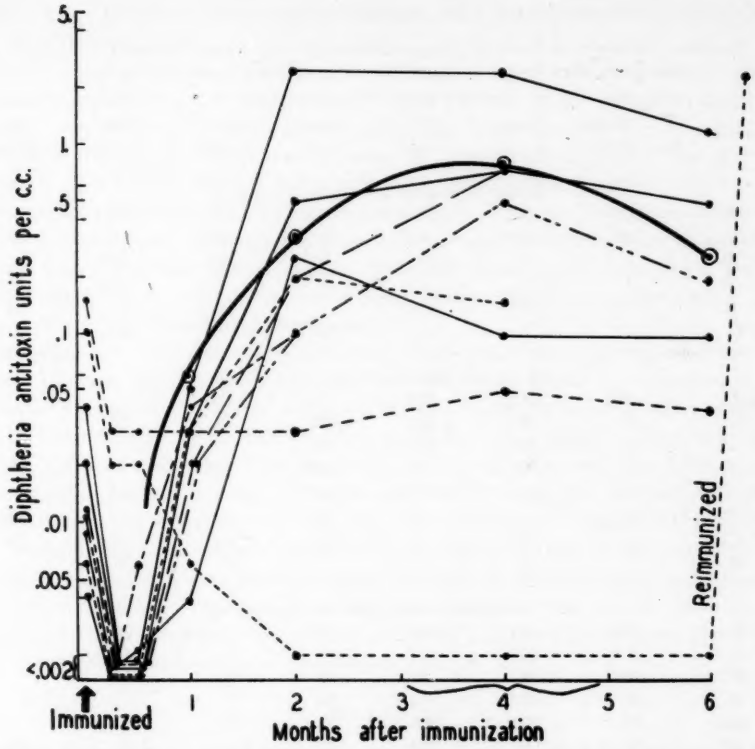

CHART 3. Response to immunization of 9 infants from 2 to 6 months of age who carried passive (transplacental) antitoxin, compared with normal mean response (ringed-dot curve) of infants without passive antitoxin.

REIMMUNIZATION

Even if interference with production of circulating antibody after immunization is almost complete, this may not indicate an entire lack of immunity on the part of the infant.

In two of the infants, passive antitoxin so interfered with active immunization that six months after the injection of antigen circulating antitoxin was below measurable levels (below .002 u./cc.). These infants were reimmunized with the same standard antigen and responded with a rapid rise in titer to over 2.0 u./cc. within two weeks. This is the typical "booster" response which indicates previous active immunity and which represents at least partial protection against infection with the disease.

DISCUSSION

The phenomenon of interference with active immunization by passively received antibodies has been confirmed by many workers. The purpose of this study is to clarify some of the quantitative aspects of this phenomenon.

It is apparent from the data that the effect on active immunization (as determined by the serum antibody response) is dependent on the titer of antibody received trans-

TABLE 1

ANTITOXIN RESPONSE IN UNITS/CC. SERUM OF INFANTS WITH TRANSPLACENTAL ANTITOXIN IMMUNIZED WITH SINGLE DOSE OF 100 Lf DIPHTHERIA TOXOID (ALUM PPT.)

Infant	Titre: Before Immunization	After 1 wk.	After 2 wk.	After 1 mo.	After 2 mo.	After 3–5 mo.	After 6 mo.
			I. Infants immunized when under 2 wk. of age				
T. H.	.004	<.002	<.002	.006	.02	.03	
A. C.	.03	.002	<.002	.02	.05	.03	.03
A. B.	.2	.04	.02	.02	.04	.008	.01
B. M.	.5	.2	.15	.1	.1	.008	.008
R. G.	.5	.25	.25		.5	.04	.03
J. L.	.5	.1	.2	.04	.03	.01	.01
			II. Infants immunized when 1 mo. of age				
R. G.	.002	<.002	.002	.1	.25		
T. B.	.01	<.002	<.002	<.002	.04	.25	.5
R. M.	.1	.02	.02	<.002	.04		.03
M. G.	.1	.02	.02	.008	.006		.15
M. F.	.15	.1	.1	.03			
A. G.	.2	.1	.05	.03	.03		<.002
P. C.	.2	.05	.03	.02	.02	.04	.05
C. B.	.5	.25	.2	.2	.1	.04	
			III. Infants immunized when 2 to 6 mo. of age				
J. J.	.004	<.002	<.002	.03	.5	.75	.5
N. R.	.006	<.002	<.002	.03	.2	.15	
F. K.	.008	<.002	<.002	.02	.2	.75	
P. O.	.01	<.002	<.002	.02	.1	.5	.2
J. Dec.	.01	<.002	.006	.04	.1		
A. G2	.02	<.002	<.002	.05	2.5	2.5	1.25
A. C2	.04	<.002	.002	.004	.25	.1	.1
M. G2	.1	.02	.02	.006	<.002	<.002	<.002
R. V.	.15	.03	.03	.03	.03	.05	.04

placentally. When the titer of passively received antibody is low, there is little or no effect on the response to immunization. When the titer of passive transfer is high, the level of circulating antibody in response to immunization can be significantly depressed.

In general the curves follow a constant pattern. At first there is a sharp drop in antitoxin level immediately after immunization. This drop is much faster than the normal fall in titer of passive antibody in nonimmunized infants as calculated by Barr and Glenny.[5] It is probably related to neutralization of the circulating antitoxin by the injected toxoid.

After a variable period, the antitoxin curves tend to come upward again. This increase in antibody weeks or months after immunization must represent the active formation of new antibody in response to the antigen. Yet it is not possible to say for any one curve when the level measured ceases to represent mainly passive (maternal) antitoxin and begins to represent mainly active (infant's own) antitoxin. At many points along the curve the antitoxin titer measured may represent the sum of active and passive immunity. Even in instances where the antibody level did not rise during the entire period of observation, it is likely that active immunization took place. This was demonstrated in two cases where the antibody level was not measurable (below 0.002 u./cc.) at the end of six

months. When given a second injection of toxoid, then infants responded with a rapid high titer ("booster" effect).

To demonstrate that passive transfer can completely interfere with active immunization, it would be necessary to demonstrate that a second injection of the antigen produces an antibody curve of primary immunization rather than a booster response. This has not occurred in the authors' experience. However, it is reasonable to expect that given a sufficiently high passive transfer and a sufficiently weak antigen, complete interference can occur. It is interesting to note in comparing these data with Vahlquist's that in his series the critical level (the antibody titer above which interference becomes evident) is lower than the present authors' appears to be. This is certainly because of the weaker antigen that he used. This stresses the relation between height of passive transfer and potency of antigen in producing interference.

This study was conducted using diphtheria toxoid under particular experimental conditions. However the principles involved can easily be transferred to clinical work. In immunizing young infants against diphtheria we will frequently be faced with a relatively high titer of passively received antitoxin.[11] However, diphtheria toxoid is a relatively potent antigen, and the multiple injections used in clinical immunization schedules should easily neutralize the passively received antibodies and produce satisfactory immunization. This has been confirmed experimentally.[9] In pertussis the problem is slightly different. Here the circulating maternal antibody appears to be a negligible factor in most cases, but the antigen is also weak. Under these circumstances, immunization of infants appears to be satisfactory clinically.[12] However, if, as has been suggested,[13] the mother were actively immunized during pregnancy, the maternal circulating antibody would become abnormally high and might interfere with active immunization of the infant.

Conclusions

Twenty-three infants from 2 weeks to 6 months old, all of whom had measurable titers of transplacentally-received diphtheria antitoxin, were immunized with a single injection of diphtheria toxoid on alum.

Infants with a low level of passive transplacental antibody were able to respond as well or almost as well as infants who had no passive transfer. The formation of circulating antibody was depressed in infants with a high titer of passively received antibody.

It is suggested that the amount of interference with active immunization is dependent on the relation of the titer of passive transfer and the potency of the antigen. The application of this principle is indicated.

Acknowledgment

The authors gratefully acknowledge the aid of Dr. A. J. Vignec and the staff of the New York Foundling Hospital in making available the facilities for this study.

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SPANISH ABSTRACT

Estudios de Inmunología en el Recién Nacido

II. Interferencia de la Inmunización Activa por la Circulación Transplacentaria Pasiva de anticuerpos

Se estudio el fenómeno ya bien conocido de la interferencia a la inmunización activa del niño debido al paso a través de la placenta de anticuerpos pasivos maternos en 23 lactantes con edades que oscilaron entre dos semanas y seis meses y cuya sangre contenia antitoxina diftérica medible en el momento del nacimiento. Cada niño recibió una inyección de 100 l.f. (unidades serológicas de floculación) de toxoide diftérico en alumbre y periódicamente se midió su respuesta en anticuerpos hasta 6 meses después de la fecha de su inmunización.

Los niños que tenían un nivel bajo de antitoxina respondieron al antígeno tan bien como los que no tenían ninguna en el momento de ser inmunizados, pero aquéllos que tenían un nivel alto de antitoxinas pasivas cuando se administró el antígeno, reaccionaron produciendo un nivel mucho más bajo de antitoxina. Por consiguiente, es obvio concluir que el grado de interferencia a la inmunización activa es proporcional al título de anticuerpos maternos pasivos que tenga la sangre del niño en el momento de ser vacunado y en proporción inversa a la potencia del antígeno usado.

477 First Avenue

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

THE PRESIDENT'S PAGE

WITHIN the past few years American medicine has made tremendous strides in prestige and influence. The Academy has contributed its part to this advance. But, progress has not been gained by accident. Behind the scenes in organized medicine are many conscientious and tireless workers who, by their enthusiasm and consecrated effort, are accomplishing the tasks with which they are confronted. Committee members are often unsung heroes in the solution of problems pertaining to the furtherance of more adequate medical care for children. The individual Academy member occasionally forgets how much so many of us owe to so few in the practical application of our ideals.

For example, those of you who attended the Annual Meeting at Toronto last fall heard the panel discussion on Pediatric Education; and saw the exhibit, describing some of the aims and objectives of our Committee on Medical Education. Under the inspired leadership of the Chairman, Dr. Lee F. Hill, this group is making progress in attempting to answer some of the questions posed by the Academy Survey of 1946-48. During the current year, continuation of regional conferences throughout the United States and Canada, with emphasis upon the problems of undergraduate education, has resulted in an intelligent exchange of ideas and an opportunity for discussion unparalleled in the history of North American medical schools. The inevitable result of these discussions will be an improvement of standards for medical education. Interpretation and evaluation of new ideas, inclusion of practical and progressive concepts for the betterment of medical school curricula, requires a great deal of time and effort. Each of us has a personal responsibility to assist the Committee in this undertaking. Medical care will eventually be supervised by those medical students with whose interests we are presently concerned.

At the various regional conferences, to which have been invited medical educators, practitioners, state chairmen, and others vitally interested in Academy objectives, there have been free discussions of curriculum content, departmental organization and similar pertinent topics. Dr. Grover F. Powers, former Professor of Pediatrics at Yale, has attended many of the conferences in the role of commentator and observer. His broad experience and mature judgment will be invaluable later when attempts are made to co-ordinate the work of the Committee on Medical Education. You will be privileged to hear his report at the annual luncheon meeting in Chicago this fall. The services of Dr. Powers, and of various members of the Committee, are available for consultation with

departments of pediatrics at the various medical schools. The group is also investigating more extensive utilization of audio-visual aids in pediatric education. You will have an opportunity, at the annual meeting of the Academy in Chicago, to hear a panel discussion on this subject, which will be conducted at the Museum of Science and Industry.

Again, we have an example of accomplishment by one of our National Committees. The Study of Child Health Services and of Pediatric Education revealed certain needs. A program was devised as a means of solving those needs. Closer co-operation is already noted between practitioners and teachers. The initiative and vision of the Chairman, as well as the earnest, devoted efforts of the entire Committee on Medical Education, have aroused the respect and appreciation of the entire Academy membership. This is the type of work which is gaining for the Academy increasing recognition for leadership in the fields pertaining to child health.

WARREN W. QUILLIAN, M.D., *President*

Round Table Discussion

ERYTHROBLASTOSIS FETALIS

LOUIS K. DIAMOND, M.D., Boston, *Chairman,* and FRED H. ALLEN, JR., M.D., Boston
DOROTHEA D. VANN, M.D., Englewood, N.J., and JOHN RAY POWERS, M.D.,
Baton Rouge, La., *Secretaries*

Chairman Diamond: Erythroblastosis fetalis is a variable disease, ranging in severity from fetal death in utero to a disturbance so mild as to be unrecognizable except by delicate laboratory tests. Intrauterine death is the greatest source of fetal loss. The development of kernicterus is the most important cause of unfavorable result in untreated liveborn babies. The use of exchange transfusion has resulted in the recovery of most liveborn babies, and has nearly eliminated kernicterus in a clinic where it has been used liberally.

Etiology

Erythroblastosis fetalis occurs as a result of fetal-maternal blood group incompatibility. Table 1 shows the most important blood group factors known at present. In Column I are the common names of the various genetically and serologically independent families or "systems" of blood group

TABLE 1

MAJOR BLOOD GROUP FACTORS

I	II	III
A-B-O	A B	O
Rh	D C C^w c E e	
Kell	K k	
M-N-S	M N S s	
Duffy	Fy^a	
Kidd	Jk^a	
P		P
Lewis		Le^a Le^b
Lutheran		Lu^a

factors. In Column II are shown those factors which may cause transfusion reactions or, presumably, erythroblastosis fetalis (although e, N, and Fy^a have not yet been reported as causes of erythroblastosis). The blood group factors in Column III seem not to cause clinical difficulties. At least 80% of cases of erythroblastosis fetalis are caused by "Rh" (D) incompatibility. Although D is an effective antigen, as judged by the fact that at least 75% of D-negative ("Rh-negative") individuals are sensitized by transfusion of D-positive blood, only 5% of families in which the mother is D-negative and the father D-positive ever have erythroblastotic babies. A and B, which are presumably even more effective antigens than D, cause less than 20% of the cases of erythroblastosis, although 35% of matings are incompatible for A or B. Probably no more than about 1% of babies who are incompatible with their mothers in the A-B-O blood groups develop erythroblastosis fetalis on that basis. Erythroblastosis caused by other blood group incompatibilities are uncommon, comprising no more than 5% of all cases—c, E, and Kell (K) are the most frequently involved factors in this small group of cases.

Presented at the Annual Meeting of the American Academy of Pediatrics, Toronto, Oct. 22, 1951.

Pathologic Physiology

The mother who lacks a particular blood group factor may become sensitized to it during pregnancy if her fetus has it (inherited from the father). In the case of D ("Rh"), the "negative" mother has about a 5% chance of eventually becoming sensitized during pregnancies if her husband is "positive." The anti-D antibodies which are the identifiable manifestation of such sensitization rarely can be detected in a first pregnancy, and erythroblastosis in the first pregnancy is rare on the basis of D incompatibility unless the mother has previously had a transfusion of D-positive blood. The sensitization of the mother is an active immunization. The baby is passively sensitized by transplacental passage of the antibodies which combine with the D substance in the fetal red cells, as is demonstrable by the Coombs' test in the early stages of pregnancy. By mechanisms still largely hypothetic the "coated" fetal red cells are destroyed rapidly, having an average life span of perhaps 1/20th normal. This is more or less compensated for by rapid production of new red cells, the hematopoietic system expanding greatly, especially in the liver and spleen, in the process. It is believed that when the baby is severely anemic in utero it may develop congestive heart failure—whether this is the explanation of the hydrops so commonly seen in stillborn babies is purely speculative.

Approximately 30% of erythroblastotic babies die in utero. This is much more common when the mother has a high titer of anti-Rh, but it is not known why some die in utero and others do not. The majority of babies are better off before they are born than after, seeming to have achieved a satisfactory adjustment so far as rapid blood production and clearing of the by-products of hemolysis (presumably via the placental circulation) are concerned. At any rate, the majority of liveborn babies are in good condition at birth, but many of them go rapidly downhill after birth. It is known that the serum bilirubin usually accumulates in the baby at a rapid rate after birth, that the reticulocytosis quickly disappears, that extensive edema may develop within the first 36 hours of life, and that petechial hemorrhage may develop with great rapidity. It is also known that kernicterus develops only after birth, usually not before the second day of life. About 15% die within the first 24 hours after birth, many of these being moribund at birth. By far the more important group, however, are the additional 15% who, without careful treatment, will develop kernicterus. Treatment can save some of the former group, but not all, by present technics, while kernicterus is now preventable.

Symptoms

Jaundice is the most important symptom. Absent at birth (except that some babies have yellow vernix) jaundice usually develops very rapidly, being usually quite apparent, and sometimes severe, within 24 hours. Incidentally, it can also be shown that almost all babies that we see who become jaundiced in the first 24 hours have erythroblastosis. The severity of bilirubinemia in erythroblastosis is much greater than that seen in other clinical conditions. It is more severe in premature babies and probably also in male babies. The occurrence of kernicterus is directly related to severe jaundice and high bilirubin levels, though the bilirubin may not be the actual cause of the brain damage.

Anemia, while common, is seldom much of a problem in itself, since it is so easily controlled by treatment. Rapid production of blood may prevent anemia in the first 2 or 3 days of life, and the severity of the hemolytic process may thus be masked. During the second week of life, and for several to many weeks thereafter, quite persistent (and resistant) anemia frequently results from almost complete inactivity of the hematopoietic system. This aregenerative phase is seldom dangerous, however, after the second or third week and almost always ends as soon as the need for blood is great enough.

Some degree of hepatosplenomegaly is usually present in erythroblastosis, though it is not always detectable on physical examination, even when the hemolytic process is severe.

Increasing edema and petechial hemorrhage are danger signals of bad prognostic import, the etiology of which is obscure.

Erythroblastemia is an inconstant and unreliable manifestation of the disease so far as diagnosis and prognosis are concerned.

The early signs of kernicterus are completely nonspecific, consisting usually of lethargy and disinterest in feedings. Opisthotonos in a very jaundiced baby is almost certain evidence of kernicterus and is almost invariably present, but it also is nonspecific. Extension rigidity of the arms with clenching and inward rotation of the fists is seen not infrequently in babies with kernicterus, and is rarely seen in other conditions. About 70% of babies with kernicterus die before 1 week of age and some of the rest die within the first year. Those who do not die have permanent motor

disability, usually severe, and more or less mental disability as well. Kernicterus is more common in males and much more common in immature babies. High maternal anti-Rh titer predisposes to kernicterus. There appears also to be an hereditary predisposition to kernicterus, the nature of which is not clear.

Diagnosis

The diagnosis of erythroblastosis depends, for most practical purposes, on the demonstration that the baby's red cells are "sensitized" or "coated" by the passively acquired antibody. When the disease is caused by Rh incompatibility, the Coombs' test is invariably positive if properly performed. The Coombs' test is positive also in erythroblastosis caused by C, c, E, and Kell. For reasons as yet unknown the Coombs' test as ordinarily done is negative in cases of erythroblastosis caused by A or B incompatibility—in these cases the appearance of jaundice in the first day of life, with serum bilirubin rising to levels above 10 mg./100 cc., the negative Coombs' test, and the demonstrated incompatibility between baby and mother are the important data. Anemia and hepatosplenomegaly are ordinarily not detectable in these cases during the critical first 2 days when exchange transfusion

TABLE 2

INCOMPATIBILITIES THAT MAY RESULT IN ERYTHROBLASTOSIS

Group of Baby	Group of Mother
A	O
B	O
A or AB	B
B or AB	A

may be necessary to prevent kernicterus. Table 2 shows the blood types of baby and mother that may be seen in such cases, in descending order of frequency.

TREATMENT

Dr. Allen: The most important function of treatment is to control the hemolytic process, as this is the principal, if not the only source of all the trouble. Infusions of blood correct anemia with little difficulty, and presumably have a tendency to help slow down the production of new cells, but the baby's own cells are still there and continue to be hemolyzed. Simple infusions also can only increase the blood volume, whereas the most anemic babies, who would need the most infusions, frequently need to have their blood volume reduced rather than increased. Exchange transfusion corrects anemia more quickly and easily than small infusions, and the blood volume of the baby can be adjusted at will in the course of the procedure. Most important, however, exchange transfusion usually removes about 85% of the baby's circulating red cells and thus brings about an immediate decrease in the hemolytic process. As further evidence of this decrease in rate of blood destruction, the babies who are treated by exchange transfusion become much less jaundiced than babies not so treated. In addition to removing about 85% of the circulating red cells, exchange transfusion removes about 25% of the anti-Rh antibody, and more important, perhaps a third of the total bilirubin. Finally, another possible function of exchange transfusion is the removal of other noxious products of red cell breakdown as well as the supplying of such protective substances as seem to be present in the blood of women.

Exchange Transfusion

There are a number of technics for performing exchange transfusions, all equally efficacious in trained hands. We have used the umbilical vein in nearly 600 exchange transfusions, in babies ranging in age up to 6 days. A single polyethylene tube is used, the business end being nearly enclosed by a special steel cannula that makes an airtight junction with the tubing and provides stiffening that allows the end of the tubing to be manipulated. Two three-way stopcocks provide a closed system which connects a syringe with the baby, the donor blood, or a waste tube. The umbilical cord is cut off about ½ inch from the skin, the plastic tubing is inserted, with the cannula, to a distance of 2 to 3 inches into the umbilical vein, and a tie is placed with a single tight knot around the stump of the cord. The venous pressure is measured, and about 20 cc. of blood are withdrawn. If the venous

pressure is normal (6 cm. of blood, or less, measured from the abdomen just above the umbilicus by holding the plastic tube against a ruler), the same amount of blood is given. If the venous pressure is high, no more than 10 cc. are put in, and the deficit is increased in successive steps until the venous pressure is normal or until a deficit of about 80 cc. has been established. Thereafter, even amounts are exchanged. Every 100 cc., calcium gluconate is given through the tube after rinsing it out with a little saline (usually 1 cc. of 10% calcium gluconate is given after each 100 cc. of donor blood).

There are a number of important details which have been covered in a paper on this subject (New England J. Med. **244**:39, 1951) but a few are important enough to re-emphasize. Gentleness in handling the cord and introducing the plastic tubing is essential, not only to avoid possible rupture of the vein, but because nothing is accomplished by force. In withdrawing blood, vigorous suction with the syringe almost always causes the vein to collapse—gentleness is again essential. The stopcocks require rinsing at intervals because of the formation of small clots within them. This is conveniently done after each administration of calcium. When the plastic tubing is disconnected from the stopcocks it must be watched constantly to make sure that air is not sucked into the baby's circulation. Calcium must be given slowly. In small or very sick babies the increments should be less than 20 cc. in order to avoid temporary circulatory overloads.

Following the exchange transfusion, the cord may be kept fresh by the application of a wet dressing that can be kept wet with weak aqueous solutions of zephiran. Penicillin, 100,000 units daily for 2 or 3 days, is given routinely, and sodium sulfadiazine, also parenterally, in divided doses to a total of about 125 mg./kg. body weight.

The blood used for exchange transfusion must be compatible with the mother as well as with the baby. Group O blood is most satisfactory because it can be obtained ahead of time and be available when the baby is born. The best cross-match test is to incubate the donor cells with the mother's serum (before the baby is born) and check the result, if agglutination is absent by the routine method, by performing a Coombs' test on the donor cells that have been exposed to the mother's serum. If these criteria for selection of the donor blood are followed, it will always be D-negative when the mother has anti-D, Kell-negative if she has anti-Kell, etc., and will not be subject to rapid destruction in the baby's circulation. Freshness is a highly desirable quality in the blood because it will undergo less initial hemolysis than older blood. We try not to use blood more than about 5 days old and prefer blood taken the same day. When a repeat exchange transfusion is planned, it is our policy to bleed a donor just before the transfusion. Women donors are preferable to men donors, especially for initial transfusions of sick babies, for reasons still not known. Whole blood is used rather than blood concentrated by the removal of plasma, because the larger the volume used the more complete the exchange will be. Except in babies weighing over 3.6 kg., a single unit (500 cc.) of blood is used.

An essential part of adequate treatment is advance preparation. This implies prenatal serologic testing of the mother for her blood groups and blood groups antibodies, blood ready in the bank for exchange transfusion, a complete set of sterile instruments and dry goods, an adequate heated receptacle for the baby with oxygen and suction at hand, and a pediatrician present in the delivery room when the baby is born prepared to do exchange transfusion and able to do the Coombs' test. All this requires considerable effort and cooperation on the part of obstetrician, blood bank, nursing staff, and pediatrician, but the results that can be obtained are well worth it.

If maximum benefit is to be obtained from exchange transfusion it must be done promptly, since jaundice is controlled much more effectively by immediate exchange transfusion than by one done some hours after birth. This is not to infer that exchange transfusion should not be done on a baby that is 12 or 24 or 36 hours old, but it is better to do it early. One exchange at birth is often better than 2 done after 24 hours. Our indications for exchange transfusion at birth are at present as follows, in the baby with erythroblastosis fetalis (Coombs' test positive): (1) clinical evidence of disease on physical examination (this is an urgent indication), (2) immaturity—less than 38 weeks' gestation, (3) bad past history—in particular, kernicterus in a previous baby or (4) prenatal maternal anti-Rh titer of 1:16 or higher. Any one of these indications is considered sufficient. In addition to the above, a cord blood hemoglobin below about 15 gm./100 cc. is an indication in itself. Repeat exchange (or first exchange in babies not done at birth) is performed if jaundice is severe or increasing rapidly, or if the serum bilirubin level is above 20 mg./100 cc. or appears to be going to go that high. Third exchange transfusions may be done, but seem but rarely to be necessary. The umbilical vein is used

again, the cord stump being cut off entirely if it has dried up, and the vein being closed at the end by a purse-string suture.

Results

The results of the program just outlined, which has been in effect for 2½ years, are presented in table 3.

The time periods were arranged so that period 2 starts with the beginning use of exchange transfusion. Period 3 begins with the adoption of our present criteria. The important change shown by these figures is the reduction in kernicterus, which has been absolute as well as relative. We feel sure that the liberal use of exchange transfusion is the principal reason for this improvement in

TABLE 3

Results in Erythroblastotic Babies Presented for Treatment within 24 Hours of Birth

	1/1/45 to 10/31/46	11/1/46 to 3/31/49	4/1/49 to 6/30/51
Total Cases	78	199	257
Recovered, no sequelae	38 (49%)	153 (77%)	225 (87%)
Kernicterus	26 (33%)	20 (10%)	4 (2%)
Died, no kernicterus	14 (18%)	26 (13%)	28 (11%)
Cases per year	42	82	114
Kernicterus per year	14	8	2
Exchange transfusion	0	73%	86%
Multiple exchange transfusion	—	0	20%
Female donor	—	16%	82%
Gestation less than 38 wk.	50%	47%	25%

results, but do not doubt that the decreased frequency of early induction of labor which is reflected in the lower immaturity rate has also played an important part.

Other Aspects of Treatment

The use of ACTH and cortisone in the treatment of erythroblastosis is under investigation in other clinics. It is still in the early experimental phase, and so far has been disappointing, though interesting.

Treatment of the late anemia consists only of small transfusions of whole blood or concentrated cells as needed. Iron and liver appear to be of no value. Small transfusions are not usually necessary after the first 2 weeks, especially in those babies who were treated by exchange transfusion, and the tendency has been to overtreat this phase of the disease.

Prevention of erythroblastosis fetalis is the hope of the future for the 40% or so of erythroblastotic babies who die in utero or in the first few hours of life and who are, for the most part, beyond the help of any present treatment. To date mothers have been given unsuccessfully vaccines, ethylene disulfonate, liver extract, methionine, hapten® and cortisone. The problem is under investigation in many clinics and could well be solved in the future. At present the promising approach would seem to be a search for something that would minimize the effect of the anti-Rh on the baby's red cells rather than a search for something that would lower the mother's titer.

Early induction of labor was practiced in this clinic more or less as a routine in the worst 50% of cases over a period of about 3 years prior to 1948. The results were poor in terms of fetal salvage and the kernicterus rate was very high. During this time exchange transfusions were done less frequently but we cannot say that the results would have been satisfactory under the present policy of doing exchanges, although we can be sure that they would have been better than they actually were. Prematurity imposes risks beyond those inherent in erythroblastosis fetalis, but most important is our knowledge that the premature baby can do less to help itself so far as clearing bilirubin is concerned than can the mature baby. They get much more jaundiced, and successful exchange transfusion therapy is much more difficult in them. Our present policy is not to induce labor in these women on any sort of routine basis. In a few selected cases, when there is a past history of stillbirth or sick baby, and particularly when fetal activity is becoming less, induction is considered at about 38 weeks.

Elective section is postponed to about 39 weeks if possible. Section is not elected on the basis of Rh-sensitization alone.

Discussion

Question: Since the degree of jaundice is so closely related to the occurrence of kernicterus, how can we explain the fact that kernicterus does not occur in bile duct obstruction?

Answer: We wondered for a long time why babies with congenital atresia of the bile ducts did not get kernicterus and were astounded to realize when we looked it up that these babies do not have high bilirubinemia; the average is less than 10 mg./100 cc. The average bilirubin in erythroblastosis is over 15, and many go to 50 mg./100 cc. or higher. Then, of course, there is the question of whether a baby who is 2 or 3 weeks old (as the babies with bile duct obstructions are when they get jaundiced) can develop kernicterus. We don't know that.

Question: Please discuss the advisability of breast feeding of an Rh-positive infant with or without erythroblastosis fetalis by a mother with the antibodies.

Answer: It has been pretty well shown in animals and in babies that after the first 48 hours, antibody proteins are little, if at all, absorbed through the intestines. Animals may develop erythroblastosis due to the feeding of antibodies within the first 48 hours. After that even feeding a potent anti-rat serum to a baby rat does not produce erythroblastosis. Feeding potent anti-ass serum to baby mules after the first 48 hours doesn't produce erythroblastosis, but during the first 48 hours the antibodies are absorbed and hemolytic anemia results. We have allowed our babies with erythroblastosis to nurse after 48 hours and have seen no ill effects from it.

Question: When the maternal Rh antibody titer is above 1:16, is exchange transfusion indicated even though the infant shows no clinical or hematologic evidence of erythroblastosis?

Answer: It has been our policy for some time to do exchange transfusion at birth in such a baby, having first proved that the baby has erythroblastosis by finding that the Coombs' test is positive. This policy will undoubtedly change somewhat in the future as we learn to tell which of these babies will be in no danger of getting kernicterus if left untreated. Our present policy is based on the statistically significant danger of kernicterus in such babies even when they are mature, when there is no past history of kernicterus and when no clinical signs of erythroblastosis are apparent at birth. When such a baby is not seen until it is 12 to 24 hours old, exchange transfusion would not be done unless the baby were jaundiced or had other gross evidence of erythroblastosis, since kernicterus is unlikely to occur in an erythroblastotic baby in whom jaundice is not evident by the age of about 12 hours. It boils down, in cases where there are no clinical signs at birth, to trying to guess whether a baby will become markedly jaundiced if exchange transfusion is withheld. A maternal titer of 1:16 or higher carries quite a high risk of severe jaundice.

Question: How long may the aregenerative phase of the anemia continue after an exchange transfusion before you become worried?

Answer: As long as the infant is doing well, gaining weight, eating and sleeping well, and not acting fussy, we would continue not to transfuse the infant because most such infants will recover before the end of the second month. The hemoglobin not infrequently goes down to 7 or 6 gm./100 cc. while the baby continues to do well and actually seems to be getting pinker rather than paler. Transfusions tend to delay, rather than to speed the ultimate recovery, and should not be given unless they are needed.

Question: Do you give those babies any iron or liver?

Answer: We have not given liver at all and iron only rarely, in the past 3 years.

Question: Has B^{12} helped at all?

Answer: We haven't any experience with it.

Question: Would you please say something about the Coombs' test?

Answer: I think it is fair to say that the pediatrician who is going to do exchange transfusions in babies with erythroblastosis should be able to do the Coombs' test with confidence. It is an extremely simple test technically, although there are some pitfalls, and one must have experience with it or he will get the wrong answers. False negatives are more frequent than false positives. The principle of the Coombs' test is this: the antibody which is called Coombs' serum is a rabbit antibody, formed by rabbits, by injection into them of human serum containing human globulin. The antibody that the rabbit produces is an anti-human-globulin, a nonspecific antibody in the sense that any human globulin will combine with it and will neutralize it. In erythroblastosis, the human globulin involved

is usually anti-Rh which is attached to the baby's red cells. The first step is to wash the red cells of the baby thoroughly—for 2 reasons: (1) to get rid of the baby's normal globulin which will neutralize the Coombs' antibody and (2) to get rid of the anti-Rh antibody except that which is firmly attached to the baby's red cells if the baby is Rh-positive. Having washed the cells thoroughly (3 washes in large volumes of saline), add a drop of Coombs' serum, centrifuge the tube, and look for agglutination. Agglutination means a positive Coombs' test, and a positive Coombs' test in a newborn baby indicates that the baby has erythroblastosis. We have seen one 6 day old infant with a positive Coombs' test who did not have erythroblastosis. He had acquired hemolytic anemia. That is the only exception to the general statement that positive Coombs' test in a newborn baby means erythroblastosis. The serum is available from a number of commercial sources; they are all satisfactory and will be better as the years go by.

Practice in performance of the Coombs' test may be had by setting up "indirect" Coombs' tests. Take a drop of Rh-positive blood in 2 cc. of saline, add 2 or 3 drops of potent anti-Rh slide-test serum, let them sit around for a half-hour and the cells will behave just like the cells of the newborn erythroblastotic baby, as far as the Coombs' test is concerned.

Question: Is the Coombs' test always positive in erythroblastosis?

Answer: By definition it is in erythroblastosis fetalis caused by Rh incompatibility, whether or not there are clinical evidences of disease, and the small group which have no clinical evidence we refer to as "erythroblastosis fetalis—no clinical disease." There is one group of erythroblastotic babies in which the Coombs' test is always negative in our experience, and that is the group in which the disease is caused by anti-A or anti-B—these comprise 10 to 20% of our cases of erythroblastosis.

Question: Is the bilirubin test a simple procedure?

Answer: It is a relatively simple procedure and takes about a half-hour to do. We need a more rapid method for doing bilirubin tests because it is possible that the serum bilirubin will be shown to be a useful guide in deciding whether to do exchange transfusion at birth.

Question: What is the total time allowed for completion of the exchange transfusion?

Answer: We try to spend at least an hour and a quarter or an hour and a half for the 500 cc. transfusion. It is usually easy to do it much more quickly than that from the technical point of view, but probably undesirable from the baby's point of view.

Question: Do you wait one minute between the inflow and outflow?

Answer: We don't wait at all because there seems to be no advantage in doing so. The donor blood is almost surely thoroughly mixed with the circulating blood as soon as it gets in.

Question: What is the procedure in a baby who had an adequate exchange transfusion and as so often happens, continues to develop increasing anemia? Do you give a second exchange or a small transfusion?

Answer: Increasing anemia during the first week, in a baby who has had an exchange transfusion, must mean that the blood was incompatible, for example, Rh-positive instead of Rh-negative. During the third and fourth weeks increasing anemia is expected and is treated with small transfusions if necessary.

Question: How rapidly do you expect the jaundice to diminish in a severely jaundiced baby?

Answer: In untreated erythroblastosis marked jaundice in the first few days is frequently followed by persistent jaundice of an obstructive type which may last for many weeks. This has been rare in the babies treated by exchange transfusion within the first 24 hours of life. It appears that the mature baby whose serum bilirubin is not allowed to go above about 20 mg./100 cc. will rapidly clear its jaundice after about 48 hours. Premature babies may not start to clear their jaundice until 4 or 5 days of age. The principal role of exchange transfusion with respect to jaundice seems to be that of preventing too great an accumulation of bilirubin during the first 48 hours.

Question: I would like to ask a question with regard to certain types of exchange transfusion reaction. I have in mind a baby who had erythroblastosis and was given 1 or 2 small transfusions in the first week or so of life. Anemia was controlled and the jaundice disappeared. At about 5 or 6 weeks of life when he came under my observation I noticed over a period of 10 days a progressive loss in blood count and I did elect to give him another transfusion, which was probably ill advised on the basis of what Dr. Diamond has said. But my point is, the blood was carefully matched with the baby's beforehand, it was Rh-negative type O blood; the baby developed an acute edema, became cyanotic immediately after the transfusion was finished, and died within a matter

of minutes. His blood was perfectly matched after death and there was no agglutination seen in his blood. I wonder what type of reaction that might have beeen and whether you think it was due to blood group incompatibility.

Answer: It is practically certain that this was not a hemolytic blood transfusion reaction on the basis of blood group incompatibility. It might have been an allergic reaction based on antibodies passively transferred with one of the earlier transfusions. It could also have been the result of circulatory overload.

Question: On 2 or 3 occasions when we were doing umbilical vein transfusions we got a thin yellowish material out of the "umbilical vein." I wonder if you have run into that? We never got enough to determine whether it was peritoneal fluid or urine or what. What do you think it is?

Answer: We also have had that experience. Obviously the plastic tubing is not in the umbilical vein but probably has been tracking along in the general course of the umbilical vein but outside of it. It is easy to create a false passage. If the umbilical cord stump is in poor condition, it is advisable to cut it off completely and pick the vein up at the skin margin.

Question: In these very sick children which I am interested in, how much blood do you take out usually without putting any in? Do you remove the blood, stop, wait, and then go ahead with the exchange?

Answer: In a sick baby with a high venous pressure we take out 20 cc., put in 10 cc., take out 20, put in 10, and continue in this fashion without any waiting, following the venous pressure at frequent intervals. The largest deficit so far was 100 cc. in a very sick baby who made a startling recovery. That doesn't seem so drastic in a sick baby when one realizes that the baby may get a transfusion of as much as 100 cc. blood from the placenta within a minute or 2 after he is born. Ordinarily, the babies respond well with a much smaller deficit. One must be cautious about removing too much blood and follow the venous pressure carefully. A deficit should not be carried in a baby whose venous pressure is less than 6 cm. of blood at the start, since it is easy to throw a baby into oligemic shock, and when that happens the venous pressure may go up instead of down.

Question: Do you worry about anemia after removing so much blood from the baby?

Answer: No. They don't become any more anemic than the other babies.

Question: What is the significance of increasing maternal titer?

Answer: It can be assumed to mean that the baby is Rh-positive, but that is about the only assumption that can be safely made.

Quesion: We have made an observation in obtaining a history as to what the fetal activity has been in the mother during the last trimester of pregnancy. We found that the fetal activity has been excellent up to the time of delivery in the normal pregnancy. However, when fetal activity has been found to decrease the infant is sometimes ill with severe erythroblastosis fetalis, or abnormalities such as diabetes or congenital heart disease. What is your reaction about inducing labor with decreasing or absent fetal activity?

Answer: Labor has been induced in some of these cases at the Boston Lying-in Hospital, and some sick babies saved that one would suppose would have been dead in utero in a few more days. On the other hand, in one case in which fetal activity had decreased and finally stopped entirely, with no fetal heart audible, the mother delivered a perfectly healthy Rh-negative baby. The decision is usually a difficult one at best, particularly since even slight degrees of immaturity—anything less than 38 weeks' gestation—carry an increased risk of kernicterus.

Question: What is the advantage of the term "icterus precox"?

Answer: Icterus precox is a designation used for erythroblastosis due to A-B-O incompatibility. The use of a different designation such as this would seem to imply a fundamental difference in the disease process. Actually there are striking differences. Stillbirth is rare, and anemia is seldom a problem, in erythroblastosis caused by A-B-O incompatibility. However, the fundamental process is the same, and kernicterus seems to have approximately the same frequency as it does in erythroblastosis caused by Rh-incompatibility. We don't use the term and would argue that its use is misleading.

Question: Is there such a thing as physiologic jaundice? Have we misclassified some of these babies, and are we doing a lot more exchange transfusions than are necessary?

Answer: There certainly is such a thing as physiologic jaundice, which, as Dr. A. Ashley Weech and others have shown, results from a temporary failure of the liver to clear the bilirubin that results from the normal breakdown of red cells in the normal baby. This temporary failure to clear

bilirubin lasts 2 or 3 days longer, and results in higher bilirubin levels, in prematures than in full term babies. The high bilirubin levels in erythroblastosis fetalis result from the similar failure to clear the much larger amounts of bilirubin that result from the rapid breakdown of red cells. In normal babies, the bilirubin rarely if ever goes above 10 mg./100 cc. in the first 24 hours of life, and they are rarely if ever jaundiced in the first 24 hours. Many normal babies are jaundiced at 2 or 3 days of age, but jaundice in the first 24 hours should always be considered abnormal and is, in Boston at least, almost always a sign of erythroblastosis fetalis. We know that we are doing some unnecessary exchange transfusions, but even in retrospect it is difficult to be sure which babies did not need them. We do know that we have practically eliminated kernicterus and are satisfied that a number of "unnecessary" exchange transfusions was a small price to pay. As time goes on we will without doubt be able to make more accurate prognostications in the individual cases and save ourselves some labor as far as exchange transfusions are concerned. At the present time it is our feeling that, countrywide, far too few exchanges are being done rather than too many.

Question: Would you describe the Coombs' test for cross match? Also what is the pathogenesis of the kernicterus? You mentioned that you thought it was due entirely to the jaundice.

Answer: The donor cells and the recipient's serum are incubated together for at least 30 minutes, in a small test tube, in the usual manner. If the cells are not agglutinated at this point the Coombs' test may be applied. The cells are washed 3 times, the Coombs' serum is added, the tube is spun down, and the cells are then re-examined for agglutination. If agglutination is present the donor blood is incompatible. If incompatibility is demonstrated by the usual technique, the Coombs' test is superfluous. The Coombs' test is really just a sensitive method.

Question: Do you routinely do the matching of both the mother's serum and the baby's too?

Answer: No. If you have the mother's serum it is preferable to use it. Using the baby's serum cannot be counted on for the cross match either in the A-B-O group or Rh because the antibodies in the baby may be completely absorbed onto its red cells, with none at all in the serum. Obviously, however, compatibility with the mother's serum is not the only criterion for selection of the donor blood, which must also be compatible with the baby in the A-B-O group. For example, group A blood must not be given to a group O baby, even though it is compatible with the group A mother. As far as the pathogenesis of kernicterus is concerned, that is still a problem that is being investigated actively by a fairly large group. What we can say is that there is a close relationship between the amount of bilirubin or jaundice and the occurrence of kernicterus. We have never seen kernicterus in a baby that wasn't quite jaundiced. Although bilirubin has not been proved to be the cause of kernicterus, it has not been proved otherwise, and so far the level of serum bilirubin is more closely related to the incidence of kernicterus than anything else that has been accurately measured.

Question: How long does the Coombs' test in the baby remain positive?

Answer: Ordinarily not more than 2 or 3 weeks in the untreated baby. Of course it is negative following exchange transfusion of the proper kind of blood but may come back positive at some later time. In untreated babies with erythroblastosis a positive Coombs' test has been reported as late as 6 months of age. Those babies undoubtedly have had a high titer of anti-Rh antibodies.

Question: In the colored baby, jaundice is sometimes very hard to determine. In those cases is it best to watch the bilirubin? Also, does the maternal antibody titer stay high for some time following pregnancy?

Answer: Actually, serum bilirubin testing is far more valuable than visual estimation of jaundice in any baby, white or colored. There is a lag in the development of skin jaundice which makes comparison of visible jaundice and serum bilirubin quite impossible, aside from the other difficulties in visual estimation of skin color. So far as the persistence of high titers is concerned, it is an individual matter with the woman. Some women will have a titer that remains constant for years and years. Usually, the titer falls fairly rapidly after the baby is born, but practically never to zero, and it is well to remember that antibodies may persist for life. We have one woman who, 40 years after her last pregnancy, has an anti-Rh antibody titer of 1:8. When we tested her 10 years ago she had a titer of 1:16 and the idea of waiting until the titer falls is of course useless in advising a woman whether to try another pregnancy, because it may not fall at all.

Question: How is calcium gluconate administered?

Answer: Intravenously. Use 1 cc. of saline to flush out the blood and then put in the calcium very slowly.

Question: Is kernicterus pathognomonic of erythroblastosis or do you see it in other conditions?

Answer: We see it very rarely in other conditions. Dr. Zuelzer, in Detroit, sees it more often than we do in babies who do not have erythroblastosis. He sees a lot more Negro babies than we do and maybe that is part of the explanation, since many of his kernicterus babies were Negroes. Our pathologists, over about a 15 year period prior to 1945, did collect a series of more than 20 babies with kernicterus who seemed not to have had erythroblastosis. Whether we would find antibodies in some if we examined the mothers' serum we don't know. Certain of them were prematures who had sepsis. Possibly the explanation for our seeing only 1 or 2 such cases in the last 7 years is the relative infrequency of prolonged and severe infections since the availability of chemotherapy.

Question: Would you discuss the hemorrhagic features in severe cases and the use of vitamin K?

Answer: There have been no important hemorrhagic features in babies treated adequately by exchange transfusion. Petechiae will not infrequently have developed before the transfusion is well started, but no new ones appear and the old ones quickly disappear. The etiology of these hemorrhages is still obscure, but they appear almost exclusively in the really sick babies. So far as treatment is concerned, we long ago stopped using vitamin K. The exchange transfusion works, either by removing the noxious agent that was responsible, or by supplying the missing factor that is needed.

Question: Where may the sets for exchange transfusion be obtained?

Answer: Your local medical supply house can get them. Becton-Dickinson manufactures most of the items. The plastic tubing is distributed by Clay-Adams. If your own dealer has trouble getting what you want, the entire set may be ordered by mail from E. F. Mâhady Co., Boston.

Question: Is the plastic tubing pushed in beyond the cannula after the exchange transfusion is started?

Answer: When the equipment is assembled, the plastic tubing is allowed to protrude about 0.3 cm. so that the leading point is the soft plastic instead of the hard steel. If blood cannot be withdrawn easily when the cannula is inserted up to the hub, nor at any place short of that point, and gentle traction on the cord tie does not help, it is proper to withdraw the cannula about 1 cm., loosen the threaded end, push the plastic in about 1 cm., and try again. If the plastic tube is inserted more than 1 or 2 cm. beyond the tip of the cannula, which is about 6.3 cm. long, the tubing is likely to end up inside the heart, which is probably undesirable.

Question: What anticoagulant do you use in preparation of the blood for transfusion?

Answer: The standard ACD solution.

Question: Have you ever seen erythroblastosis fetalis in only one of identical twins?

Answer: No. By our definition, that a positive Coombs' test makes the diagnosis, such a thing would be impossible on theoretic grounds. We have, in fraternal twins, seen one stillborn with hydrops fetalis and the other apparently normal at birth. In this case the 2 halves of the placenta looked as different as the babies did. The baby that looked so well at birth had erythroblastosis too, became severely jaundiced, developed kernicterus and died. This happened before the days of exchange transfusion, and we are confident that he could have been saved by present treatment. We have seen similar though somewhat less striking differences in other sets of twins, which indicate the striking degree of variability that is possible in this disease, based probably on inherited differences in vulnerability.

Question: Is it possible for an Rh-negative baby to stimulate a rising titer of Rh antibodies in a previously sensitized woman?

Answer: Probably not, but such are the inherent errors in antibody titration that the titer may seem to go up in occasional cases unless tests are run simultaneously on successive serum samples that have been saved in the frozen state.

Question: How can we explain the reported cases in the literature of kernicterus in premature babies who had very little jaundice?

Answer: This question brings up a number of points. The cases referred to were shown not to be cases of erythroblastosis. We can now be sure that in mature babies with erythroblastosis kernicterus does not occur in the absence of marked jaundice. Premature babies may well be more vulnerable to bilirubin, or whatever it is that causes kernicterus, and so develop kernicterus with relatively little jaundice. Studies which might answer such questions are badly needed. We have been greatly impressed, however, with 3 other things. One is the paucity of factual data with regard to jaundice on nursery records in general, including those of our own hospitals. We have seen extreme jaundice in a 3 day old baby which must have been quite marked for at least 48 hours, but no note of it was in the record. Second is the casual attitude which most nurses, and doctors too, have toward jaundice

in the neonatal period, which probably reflects what they have been taught. The lack of notes and the casual attitude result in jaundice actually not being "seen." In our experience one has to really watch for jaundice or risk being very much surprised. Thirdly, the degree of skin jaundice lags way behind the rising level of serum bilirubin, which further adds to the difficulty of observing jaundice in a plethoric newborn who may be lying in the bottom of an incubator in very poor light. We have not, in the past 7 years, encountered a case such as those you referred to, so we can only speculate, and our thoughts are that premature babies may be more susceptible to kernicterus, and that the jaundice in those reported cases may have been greater than the records indicated.

Question: What is the explanation that kernicterus does not complicate adult jaundice? Are the pigments formed in the premature or newborn infant chemically different—possibly related to the differences between fetal and adult hemoglobin?

Answer: All we know for sure is that the bilirubin levels in erythroblastosis, which may be as high as 60 or 70 mg./100 cc. are higher than the levels seen in the jaundice of adults. Again we wonder if the newborn nerve cells are more susceptible than those of adults. The thought about possible chemical differences in the pigments has received some attention, but we are not aware of any reports that indicate that there are any differences. Of course, the bilirubin in erythroblastosis is known to be practically all of the indirect variety, whatever that really means.

Pediatrics

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

This issue contains an address by Dr. Paul B. Magnuson, Chairman of the President's Commission on the Health Needs of the Nation. It was given at the annual meeting of the Medical and Chirurgical Faculty of the State of Maryland, and through their courtesy is published concurrently with its appearance in the Maryland State Medical Journal.

"TOO BIG A JOB FOR ONE YEAR"

By PAUL B. MAGNUSON, M.D., LL.D., D.Sc.

When I received your kind invitation to give the annual Trimble lecture, I wrote Dr. Compton that I had several pretty sound medical papers worked up on the causes of pain in the lower back—I've been working in that field for more than 40 years—but that the ladies might be much more interested in some information on the President's Commission on the Health Needs of the Nation. So, in deference to the ladies, I am going to talk about the latter topic.

Last November, without a word of warning I got a call from the White House that the President of the United States wanted to see me. I took the train from Chicago that night, and the next morning met with the President. The President laid the cards right on the table. He said he was deeply concerned with the health of the American people in these trying days of all-out-mobilization. He said he had made certain proposals to bring more and better medical care to the people, but these proposals had precipitated an emotional argument which clouded the issue. The President said he was not necessarily committed to any one plan—if any group could come up with a better series of proposals

than the ones he advocated, he would be the first to support them if they would insure better health for all the people.

For that reason, he said, he had decided after long deliberation to set up a Presidential Commission to get at the facts. He offered me the chairmanship, and promised me an absolutely free hand in choosing the members of the Commission.

For the record, I want to say that I had absolutely no interference or pressure in selecting this Commission. All the members were suggested by me to the President after I considered their interests, ability and fairmindedness. No one in the White House ever raised a question as to whether an appointee was a Democrat or a Republican, or whether he was in favor of the President's plan or not. Maybe I'm prejudiced, but I think this is the best of a long line of Presidential Commissions. It is absolutely free of politics; we have laid down a rule that no one from a Government agency shall be in any policy-making job.

Of course, we have an awfully big job ahead of us. Let me read you just a bit from the Presidential directive.

The Commission has one major objective, the directive reads. "During this crucial period in our country's history, it will make a critical study of our total health requirements, both immediate and long-term, and will recommend courses of action to meet these needs. The Commission is authorized and directed to inquire into and study the following:

(a) The current and prospective supply of physicians, dentists, nurses, hospital administrators and allied professional workers; the adequacy of this supply in terms of the present demands for service; and the ability of educational institutions and other training facilities to provide such additional trained persons as may be required to meet prospective requirements.

(b) The present ability of local public health units to meet demands imposed by civil defense requirements and by the needs of the general public during this mobilization period.

(c) The problems created by the shift of thousands of workers to defense production areas requiring the relocation of doctors and other professional personnel and the establishment of additional facilities to meet health needs.

(d) The degree to which existing and planned medical facilities, such as hospitals and clinics, meet present and prospective needs for such facilities.

(e) Current research activities in the field of health and the programs needed to keep pace with new developments.

(f) The effect upon the continued maintenance of a desirable standard of civilian health of the actions taken to meet the long-range requirements of military, civil defense, veterans' and other public service programs for medical personnel and facilities.

(g) The adequacy of private and public programs designed to provide methods of financing medical care.

(h) The extent of Federal, state and local government services in the health field, and the desirable level of expenditures for such purposes taking into consideration other financial obligations of Government and the expenditures for health purposes from private sources."

A mighty large order! When I met with the Commissioners in the middle of January, there was a collective sigh when I read that directive. However, we decided to go around the table and get each other's ideas on how we could tackle the job.

The Chairman led off. I told my fellow members that I had practiced medicine for forty years and still had implicit confidence in the good, common sense of the American people when a straight proposition is put before them and they are given reasons. I said it was our job to put such a sound proposition before the people. We were not promoting anything—we were trying to find out. I said I felt then, as I have felt always, that there is nothing to the practice of medicine except three things: the prevention of disease, the cure of disease, and the returning of a patient to a useful situation in life.

I told the medical members of the Commission that we could not hold to the proposition that there can be no improvement in our profession, because there has been improvement, tremendous improvement, every year. Conditions have changed a great deal since I started practicing medicine, I said, and maybe the medical profession has been guilty of denying the existence of problem areas without looking at the many sides of the question. As long as one person in this country dies needlessly of illness or disease, there is a problem.

Then I turned to the other members of the Commission—outstanding citizens from the ranks of labor, agriculture, education, dentistry, nursing, as well as medicine, and asked them for their views as to the job of this Commission. I wish I had time to quote from all of them, for they together epitomize the free-swinging, democratic spirit of this group. But I cannot resist a few selected quotes.

Walter Reuther, who came up from the other side of the tracks to the Presidency of one of the country's largest unions, made this moving statement:

"I have had the opportunity, and it was not of my choosing—to be in about five or six different hospitals during the last five or six years. I was at Duke hospital. They took care of me very well down there. I wish every American could get the kind of medical treatment I got. I think every American is entitled to it.

"If we can forget about the ideological aspects of this controversy and really talk as people, I think we will agree that the doctors of America are just like everybody else. They want to make their contribution at trying to make America a better place for people because really that is what the whole fight in the world is about. IT IS ABOUT PEOPLE. We want the kind of America where people can have an opportunity to make their contribution without any restrictions on their growth. We want every child to have the right to grow up strong in mind and body no matter what side of the railroad tracks he is born on. I believe we can look at this problem in terms of what are the health needs of America, what are our facilities to meet those needs, how large the deficit is and then sit down and say, 'O.K. This is the problem—how do free people solve that problem?' "

Clarence Poe, editor of the "Progressive Farmer," one of America's great farm journals, had this to say:

"The average man in America today knows now, more vividly than ever before, how valuable modern scientific knowledge has become in protecting the health and the life of his wife, his children and his family, and the determination to have it. It seems to me that the most important job before our Commission is finding some way, some form of insurance or some kind of help by which the poorest people of the country can get proper medical and hospital care. I imagine I speak for the farm folks on that."

And finally, some wise words from a doctor—Russel V. Lee, who has a big group clinic out in Palo Alto, California:

"I hope we will regard this activity primarily as a research product and not bring to

it too many preconceived ideas. I have worked on a similar affair in California for a year. At the end of that time, I was impressed with what I didn't know and didn't have the answers for.

"I am certainly not one of those who thinks there is no need for such activities as this. The need for this Commission's work comes curiously enough from the success of medicine and all medical activities. Up until 1910, it was demonstrable that you were just as well off if you had no medical care as far as longevity was concerned, yet every decade since that time there have been enormous advances in medicine until today it is quite likely you are much better off if you have adequate medical care. I think we have available potentially the medical knowledge and resources to make this country a heaven on earth as far as medical conditions are concerned.

"Our principal task is to point out how these resources should be applied to the problem. It is perfectly certain that most of the infectious diseases can be completely eradicated with what we have now. There is no sense in having venereal disease. A year of proper activity would wipe out syphilis and gonorrhea.

"New fields in medicine have developed with great rapidity, but that puts a tremendous obligation upon medicine. And I mean all the ancillary services, too—hospitals, nurses, technicians, etc.—to render what we have available to the public. The public is demanding it. That is something we must realize.

"I think perhaps the ordinary citizen exaggerates in his own mind the miracles that medicine can do, but when the father of a family whose children are ill believes there is available somewhere the medical knowledge and facilities to save the lives or prevent the crippling of his children, he is certainly going to demand that he get it regardless of what his social status is. He may put up with poor housing and a number of other things, but if it is life or death for his family, he will not put up with it."

All right, we have this big job. How are we going about tackling it?

First of all, The Commission has divided its work into three parts:

1. Assessing the total health resources for the country. A staff of technicians has been working on this since the middle of January—digging into the complexities of number of health personnel, hospital beds, health education facilities, health insurance coverage, costs of medical care, and so on. Sometime in the fall, the Commission hopes to bring out a monumental and important volume entitled: "The Health Resources of the American People." We think it will be the first completely factual, unbiased analysis of our total health strengths and shortcomings.

2. The second part of the tri-partite working plan, estimating the health needs of the American people, is now keeping us busy day and night. We have scheduled a series of more than 25 panels on every imaginable phase of medical care. Each of these panels is an all-day give-and-take session—no formal testimony and no ceremonial parading of witnesses. The country's ten or twelve top experts in each of the fields sit down for a day behind closed doors and bat the problem around. The panel findings are then digested and presented to the full Commission. By the time of the final panel somewhere around the last week in June, the Commission will have heard several hundred top medical and lay experts from every section of the country give their off-the-cuff views on everything from promotion of health and prevention of disease to care of the mentally ill and the status of rural medicine.

We held seven all-day panels in April, and I attended every one of them. The second

week in April, we had separate one-day panels on general practice, specialization and group practice, and I want to say to you without one ounce of exaggeration, they were the finest, most stimulating discussions of the subjects I have heard in 40 years of listening in at medical meetings. No holds were barred. As an example, on the second afternoon we had the general practitioners and the specialists come in and have at each other. You should have seen the fur fly.

We have kept up that gruelling pace since then. In the last two weeks of April, we had panels on rehabilitation, regional medical plans, promotion of health and prevention of disease. The stenographic transcript of these April meetings runs to over 2,000 pages, and we have a lot more panels to go.

And that's not all in the health needs area. Prior to these panels, the Commission held a series of formal hearings on aid to medical education and local public health units. We heard 16 experts give fact-packed testimony which filled more than 500 pages of the Commission's official records.

As a final step in estimating health needs, Commission members are now mulling over the idea of a series of field trips to get a close, realistic view of both the good and bad in medical care today. As an example, there is talk of a trip to rural Mississippi to find out just what medical care rural people get. In addition to talking to people on the spot, the Commissioners would visit country practitioners, look over local hospitals, study the state's regional medical plan, and so on. Another trip might take Commissioners to a defense-impacted area where they could observe the many problems created for providers of medical care by sudden shifts of population.

3. Finally, when all the health resources have been inventoried, and all the needs have been ascertained, the Commission will get down to the job of making its formal recommendations to the President trying, as far as possible, to fit its final proposals within the framework of the achievable health resources of the country.

Now I want to talk to you a bit about what is closest to my heart—taking care of sick people and preventing people from dying. In the five years that I was with the Veterans Administration, I had only one paramount concern—getting our veterans well again and returning them to society as useful, productive citizens. I wouldn't give you a cent for one inch of red tape in that operation, but I wouldn't take a hundred million dollars for the satisfaction I got in feeling that I helped in a small way to return thousands of veterans to good health.

It is true that we have made great strides in the past half century in the improvement of the general health of the American people. From an average lifetime of 49 years in 1900, our life expectancy has risen by more than one-third to nearly 68 years at present. This is a singular tribute to the skill and devotion of the American medical profession.

However, as my friend Walter Reuther puts it, there must be no sacred cows in American life. He points out that the workers in his union make good automobiles, but they could make better ones. In like manner, we doctors are providing good medical care, but we could provide better medical care. We are not perfect. Those few in our profession who, ostrich-like, deny the existence of any health problems do their own profession and the American people a great disservice.

Let me give you an example. At one of our Commission meetings, we heard testimony from Dr. Howard A. Rusk who, in addition to being medical director of the Institute of Physical Medicine and Rehabilitation in New York City, is chairman of the Health

Resources Office in Washington. The Health Resources Board has been making some intensive studies over the past several years of the total health requirements of the nation. Here are a few of the figures Dr. Rusk gave to the Commissioners:

1. There are estimated to be between 25,000,000 and 28,000,000 handicapped people in this country. This includes between nine and eleven million people with heart disease, probably a third of whom are severely disabled; about six million with arthritis; two and a half million with orthopedic disabilities; 1,500,000 hemiplegics; 600,000 amputees; 50,000 paraplegics, and so on down the line.

Dr. Rusk said a Health Resources task force report on rehabilitation showed conclusively that from two to four million severely disabled people could be gainfully employed if they received adequate training. He said that, with dynamic programs, 90 percent of all severely disabled persons can do some type of gainful work. For example, in a survey of some 600 paraplegic miners whose paraplegia had existed anywhere from six months to 21 years and who were accepted for rehabilitation, 80 percent were placed back in gainful occupations after an average training time of 4 months.

He told some moving stories—for example, of a boy with both hands off who was suicidal when he entered the New York Rehabilitation Institute. That boy, who has a wife and three children, is now a mechanic's helper at Sperry Gyroscope handling 40-pound boxes.

Dr. Rusk pointed out an amazing thing—out of a thousand people his Institute had trained and placed in industry in the last 18 months, only four had to be replaced.

We had the same experience in the Veterans Administration. In the Minneapolis hospital, we had 169 patients who had been bed-fast anywhere from two to fifteen years. We instituted a rehabilitation program up there with a group of doctors. It takes a group to do it—the orthopedic surgeon, whom I mention first because that is my category, the neurologist, the psychiatrist, the internist and everyone else they want to call in.

That group went to work on those 169 patients who had been in bed for so long. Inside of nine months, fifty percent of them were back earning a living. At this time, four years after the program started, only nine of those patients are still bed-fast!

Now, remember this—until this program had started, nobody had paid any attention to them, nobody had given them any help, nobody had guided them, nobody had taught them what they could do toward making a living with what they had left. Sure, it was a tough job. Many of them had arthritis, and I know arthritis hurts, but it doesn't hurt half as much when you're busy as it does when you're loafing, sitting in bed thinking about your suffering. Getting these people back to work in itself is enough to give them a new hope, and when it comes to the humanitarian side of it, it is a most important part of medicine.

Dr. Rusk also gave the Commissioners these additional findings from various studies by his Health Resources office.

2. One out of every 18 persons in the United States is now suffering from some form of mental illness, and one out of every ten persons will need psychiatric care at some time in his life.

3. About 20,000,000 people now alive will die of cancer unless new treatments and cures are found.

4. Two persons out of three in the United States need financial help to meet the costs of serious illness.

5. Sickness absenteeism costs the nation the full time of 2,000,000 workers each year.

6. The Nation's medical schools are faced with a serious financial crisis. Their deficits in 1948 totaled $10,000,000 and are running higher today.

7. Nearly 50,000 nurses over and above those now in sight will be required by 1954 to meet both civilian and defense needs.

8. Nearly 30 percent of our citizens live in communities in which there are no full-time local public health services.

When problems such as these exist, can we say there is no room for improvement? We all know of areas where a better quantity and quality of medical care can be given.

Can we do the job of surveying the health needs of the nation in the brief year allotted to us? I don't think we can do an absolutely comprehensive job, but I think we will come forth with some solid facts and recommendations in December. However, there is feeling among some of the Commissioners that this is really a five-year job which will change from year to year. If this Commission is to be of any permanent value, it should be a continuing Commission on the basis of the interest of the medical profession and the public to put all the information together that we can gather.

We need the cooperation, in our difficult task, of both the medical profession and the general public. As the *New York Times* said recently: "It would be tragic indeed if full cooperation is not given to them (the Commissioners) in their efforts."

I didn't want this job in the first place. I have had my heart set on establishing a physical medicine and rehabilitation institute in Chicago before I retire from my arduous labors, and my present duties with the Commission have postponed that work. However, I could not in all conscience refuse the President's call to duty. I suppose I've got a reputation by now as a pretty frank talker, so let me quote to you what I told the press the day I was sworn in on this job; and I now quote:

"I believe that my professional brethren know that I am interested in no way in politics. I took this position which is an unenviable one, to see if information could be gathered from all sides and all shades of opinion to make a cohesive story so that both the laity and the profession could understand the difficulties and hazards of the distribution of health services to the people of America, and to see if there is any way to improve conditions without interfering with the whole economics and ideals and progress of American medicine. I think it can be of great educational value to the American people to have a Commission discuss these things openly and freely, and without malice."

I have high hopes for this Commission. In the past few years, there has been an excess of emotion and charges and counter-charges about this whole health problem. I agree with *The Washington Post* that, in this bitter dispute, the forgotten man has been the citizen in need for more and better medical care. If this Commission can inject some light where too much heat has prevailed in the past, it will help signalize a desperately needed moving forward in bringing better medical care to all Americans.

Thank you again for the opportunity to share my problems with you.

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

BLACK MARKET IN BABIES

BY THE very nature of their specialty pediatricians as well as obstetricians are not infrequently involved in adoption procedures. Childless parents seek the help of physicians in obtaining children for adoption; unwed mothers seek ways through which their babies can be placed in a happy home; unwanted babies become available, but in numbers far too few to meet the demand for adoptions. Ignorance of State law and of agencies established to control adoption proceedings may inadvertently lead to serious consequences for parents and physician—to say nothing of the baby. Adoption is not just the placing of a baby into the hands of a couple who want it. There are recognized standards and regulations which must be observed. Assurance should be obtained that the babies are normal, healthy, and that so far as possible, the characteristics and potentialities of the baby should be matched to those of the prospective parents. Equally important, the parents should be stable and adequate to the responsibilities of rearing the child.

The extent to which proper adoption procedures are neglected or purposefully avoided has recently been brought to light in the public press in a large Eastern city. The question may reasonably be asked whether this situation does not also exist in many other areas throughout the country.

From *The Philadelphia Inquirer* of June 26, 1952, we quote as follows from a column signed by Joseph H. Trachtman:

"A huge 'black market' in babies involving the sale of newborn children into foster homes for prices ranging as high as $2500 has been uncovered by city investigators, *The Inquirer* learned yesterday.

"The District Attorney's office has uncovered clearcut evidence that doctors and lawyers are involved in the illegal traffic, and strong indications that a well-organized ring is handling a major share of the lucrative business.

"Tiny offspring of unwed mothers or of families feeling the pinch of economic hardship are being spirited from hospital nurseries or lying-in homes to eager would-be parents not only in Philadelphia, but through a wide section of the East.

"Major ramifications of the 'black market' ring are believed to extend to New York City, and the District Attorney's office has poured additional investigators into the probe on the strength of major evidence already in hand.

"The cool bargaining in new-born infants, with prices of $1000 or more reported to be common, is in direct violation of State law and has thwarted the efforts of State and city authorities to properly supervise adoption proceedings.

"Assistant District Attorney Samuel B. Gomberg, assigned to Municipal Court, is in direct charge of the investigation.

"Gomberg confirmed yesterday that the investigation was under way and said it had been pressed quietly for 'several months,' although he declined to comment on results of the probe to date.

"The 'black market' operation is believed to be centered among the nearly 200 adoptions reported to the Municipal Court annually in which there has been no official nor agency supervision.

"There were indications that several hundred additional children a year might have been placed with foster families without any effort at legal adoption and without the knowledge of the Municipal Court or other official bodies.

"Gomberg and his aides were reported ready to crack down in enforcement of State laws which provide up to $2000 fine or up to five years' imprisonment for each case of such 'black market' dealings in babies.

"The Pennsylvania law specifies 'whoever deals in humanity, by trading, bartering, buying or dealing in infant children is guilty of a felony,' with those penalties set forth in the law.

"Although Gomberg declined comment, the 'black market' operation was reported to include both doctors and lawyers, as well as a number of other persons, who had acted as 'go-betweens' for high fees in turning over babies to childless couples.

"In a typical operation called to the attention of the investigators, a young unwed mother had gone to a doctor for pre-natal care.

"Arrangements were made for her to be admitted to a hospital for the delivery of the baby.

"In the meantime, a lawyer representing a well-to-do but childless couple contacted the doctor and asked that the baby be turned over to them for eventual adoption.

"An agreement was reached for payment of a substantial fee of more than $1000, covering the young mother's hospital and medical expenses.

"As soon as possible after the baby's birth, by agreement with the mother, the child was taken from her and delivered to the childless couple. The mother signed an agreement relinquishing her right to the child. She never met the couple to whom her baby was delivered and did not know their name or address.

"Since many hospitals would provide free hospital care for prospective mothers who are without funds, investigators believe that even the payment of legitimate fees to the doctors involved can be a violation of the State law.

"In many cases under investigation, fees were reported so exorbitant as to amount almost to an outright 'sale' of the tiny baby.

"Manuel Kaufman, deputy commissioner of the City Department of Welfare in charge of children's services, said that major weakness in Pennsylvania's adoption laws left the door open to 'black market' procedures.

"Kaufman is a social worker of more than 20 years' experience. He was a consultant for the children's division of the Health and Welfare Council before assuming his municipal post and also served as director of the Jewish Social Service Agency in Washington, D. C.

" 'The law in Pennsylvania allows anyone over 21 to adopt practically anyone,' Kaufman said flatly.

"He said that under the Pennsylvania legislation even an unmarried person could adopt a child.

"Kaufman said that the Philadelphia courts had used their authority to bar such adoptions, but that there was nothing in the law to prevent the court from approving a case in which an infant was turned over to an unmarried man or woman.

"Kaufman produced statistics which showed the possible market for the sale of unwanted babies. He said that standard statistics show that one out of every seven married American couples is without children.

"Other social workers cited records compiled by the Municipal Court to show the possible scope of an adoption racket. In 1950, the last complete year for which statistics are available, the Municipal Court here approved a total of 553 adoptions.

"The total is believed to be as high, or higher for 1951.

"In this group, the court record shows, were a total of 232 adoptions approved for stepparents or other relatives. Social workers said this was a normal procedure in which relatives adopt orphan or destitute children to better provide for their care, or where step-parents use this method to cement the new family relationship.

"Another 123 children were placed with foster parents under the supervision of various institutions, the Department of Welfare or legitimate private placement agencies. The last are community social agencies similar to those which make up the Community Chest.

"The Municipal Court record also shows 121 cases in which unmarried mothers placed the children directly with the adopting family and 77 cases in which the placement was handled by other persons having no official status, some of them doctors.

"Veteran social workers said the last two classifications showed a total of 198 cases in which the children were placed with prospective foster parents without any sort of official supervision.

"The Municipal Court does not enter into these proceedings until a year or more after the baby is turned over to the prospective foster parents. This is at the time when adoption proceedings may be introduced.

"Under the law, the court is empowered to investigate the foster parents before permitting adoption of the child, but this is only after the child has been with the family for a year.

"There were indications that many of the couples to whom children were turned over did not seek adoption, so that these cases were not among the Municipal Court records.

"This could not be established to any degree pending the result of the District Attorney's office investigation under Gomberg's direction.

"The Bureau of Vital Statistics reported that 3267 children were born to unwed mothers in Philadelphia during 1951. Of these 718 were white children. Many of these children would remain with their mothers, but some percentage would be turned over to foster parents for adoption.

"The District Attorney's investigation showed some evidence that a 'ring' was operating in the baby market, it was learned, because the names of 'certain persons' had appeared repeatedly in adoption cases.

"The link to New York was indicated by the fact that Gomberg had made several trips to that city to confer with its District Attorney's office on evidence of baby 'black market' operations already uncovered there.

"Social workers and State officials were reported 'alarmed and concerned' over the conditions already disclosed by the investigators.

"State Secretary of Welfare William C. Brown has called a conference of representatives

of social agencies throughout Pennsylvania. He has asked them to recommend 'remedial legislation' which would tighten up the Commonwealth's adoption laws.

"Kaufman said that what the social agencies hope to attain is a program under which 'children will be placed in foster homes according to recognized standards.' He suggested that existing evils could be eliminated if all adoptions were handled through trained agencies and the courts."

A further article in *The Inquirer* for June 26, 1952, continued the story:

"As the District Attorney's office here was shaping up a new blow at a massive 'black market' in new-born babies, an official of a social service agency disclosed yesterday that babies are being offered up-State through 'mail-order' ads.

"This disclosure came from Walter P. Townsend, general secretary of the Children's Aid Society of Pennsylvania, who added he had heard of foster parents paying as high as $1000 for a child adopted through illegal channels.

"Townsend said that even with this flagrant display of contempt for the law it is difficult to prove a case of 'bartering in human flesh.'

" 'The foster parents won't talk and neither will the mother who sold the child,' he said.

"Townsend, whose society is the representative of adoption agencies in Philadelphia and eight surrounding counties, admitted that trading in babies 'is an acute problem that can only be licked by laws stating that adoption can be handled only through legally recognized agencies.'

"Townsend's society last year placed about 480 children in foster homes. He said his society has a waiting list of approximately 700 families.

" 'There is no question of there being a black market,' Townsend said. 'I have heard rumors that prices as high as $1000 have been paid. The law is being flaunted and the danger to all parties concerned is startling when one considers all the possible eventualities.'

"Msgr. Cornelius Brennan, head of the Catholic Children's Bureau, and Philip Sterling, chairman of the adoptions committee of the Association for Jewish Children, agreed that an amendment to the State adoption laws is called for.

"Sterling said 'there is room for improvement in the adoption law but it should be made part of a total statewide child service law. Any change of the law should include that the adoption of children be supervised by accredited social agencies only.'

"Sterling said he had 'heard rumors of people paying for babies' but added that many of the unwed mothers who sell their infants are unaware that social agencies exist to aid them in their distress.

"Monsignor Brennan, whose bureau handled 161 adoptions in 1951, said 'there is a wide, unsatisfied demand for foster children. For every child available, there are 10 applications.'

"Investigators and social service experts agreed that the demand has made it possible for the black market to operate on such a grandiose scale and at such high prices. By adopting a child through these undercover channels, prospective parents sidestep the least possibility that the adoption will be blocked."

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

POPULATION TRENDS AND PEDIATRIC OBJECTIVES*

By HENRY F. HELMHOLZ, M.D.
Rochester, Minn.

TODAY there are about 60,000 more people in the world to feed, clothe and house than there were yesterday; and tomorrow there will be 60,000 more than there are today. This continuous excess of births over deaths is more marked now than ever before in history, an excess of approximately 20,000,000 in a year. It is hardly necessary to point out here that a claim for great accuracy cannot be made for the figures given in this paper. Such as they are, however, they can support the main contention of this communication.

It is estimated that there are about 2,500,000,000 people in the world today. The population in 5000 B.C. has been reckoned at from 5 to 10 million; in 3500 B.C., from 20 to 40 million; between 1000-500 B.C. 100 million; between 100-500 A.D. 200 million; in 1825, 1 billion (1,000,000,000) and in 1930, 2 billion (2,000,000,000). The percentage increase in the years B.C. was 0.05%, from 1650-1750 A.D., 0.29% and from 1900 to 1950 A.D., 0.75%. It is estimated that at present the increase in population is about 1% a year, which figures out to an increase of 2 persons every 3 seconds, and 200,000,000 in a decade. In spite of World War II, Europe increased 20,000,000 in population from 1940 to 1950.

The balance of population is the relation of total births to total deaths. In the early days, the human race depended for its survival on a high birth rate to balance the excessively high death rate from disease, war, starvation, wild animals, and accident. It probably took four or more births per family to bring about the slow increase in population in prehistoric times. The goddess of fertility was worshipped because upon her depended the survival of the race. This inborn veneration of fertility is still a dynamic force in various world cultures today. In contrast, let me cite that an average of 2.2 children per family will keep the population constant in the United States today. Everywhere the campaign to lower the death rate meets with approval, but any attempt to lower the birth rate is met by marked opposition by those who consider parenthood a sacred right without accepting it as one of the greatest responsibilities.

In world history up to about 1800 the slow increase in population resulted from a birth rate sufficiently high to slightly more than offset the high death rate; this represents the first stage in population trends. The period was distinguished by an excessive infant mortality rate, ranging from 400 to 200 per 1,000 births. At times these rates were even higher, corresponding with world epidemics of such diseases as cholera, plague, smallpox, typhus and typhoid fever and the centuries of high death rates from malaria, syphilis, tuberculosis and other diseases.

* Read at the Latin American meeting of the American Academy of Pediatrics, Montevideo, Uruguay, Dec. 5 to 9, 1951.

It took 200 years to double the population from 1650 to 1860, but only 100 years to double the population from 1825 to 1925. This latter period represents the second stage in population trends. A continued high world birth rate and a markedly decreased death rate resulted in this rapid increase in population. Particularly since 1900, phenomenal reductions in mortality rates have been seen. From 1850 to 1900, the population of Argentina, Brazil and Chile increased, as has been estimated, from 10 million to 23 million and from 1900 to 1949, from 23 million to 71 million.

In no small measure has the pediatrician helped to reduce the number of infant deaths and almost to eliminate (by 98% in the United States in North America) deaths from the communicable diseases, scarlet fever, diphtheria, measles and whooping cough. In the last two decades, the introduction of sulfonamides and of antibiotics such as penicillin and streptomycin has reduced deaths from bacterial infections by one half to three fourths and has made possible cure of diseases that previously nearly always were fatal.

What the introduction of public health measures can do to population trends in underdeveloped areas when not accompanied by corresponding measures aimed at high gains in educational and socio-economic development is aptly illustrated by the results in Puerto Rico. For some time during the second half of last century the population of the island seemed to be rapidly approaching a stationary condition at a level of a little over 1,000,000 inhabitants as a result of matched high birth and high death rates. With the introduction of appropriate public health measures the high death rate has declined to its present level of about 10 annual deaths per 1,000 population. However, during all this period the birth rate has remained practically stationary at the high level of about 40 annual births per 1,000 population, a thing indicative of relatively slow improvement in the socio-economic conditions usually associated with high fertility rates. Were the present rate of increase to continue, the population of the island would double in 24 years, as compared with the world average which doubles in one hundred years.

A further example of what happens when death rates are markedly lowered and birth rates remain the same or increase is seen in present-day Japan. Since the end of World War II there has been a remarkable decrease in the death rate, from 29 per thousand in 1945, to 18 in 1947, and to 12 in 1948; this is the result of an intensive campaign of vaccination and immunization. At the same time, the birth rate has increased from 23 per thousand in 1945 to 34.8 per thousand in 1947 and to 34.2 in 1948. The population of Japan in 1950 was 84,000,000, as compared with 73,000,000 in 1940 and 69,0000,000 in 1935. To quote from a Japanese report of July, 1951: "The new population figure for April, 1951 shows an increase of 200,000 over March, 1951." Incidentally, both Puerto Rico and Japan must import from a fourth to a third of their food. The United States in North America spent more than $1,250,000,000 on food for Japan from July, 1948 to July, 1949.

China is still in the first stage of population trends, with a high birth rate of 40+ per thousand and a high death rate of 30 per thousand. This may be partly owing to the scarcity of physicians. China has one physician to 40,000 people; the United States in North America has one to 750. It has been estimated that 1,000,000 people starve to death each year in China and that probably ¾ of a million people die of smallpox. With regard to the production of food, it is instructive that 80% of the working population cultivate 220,000,000 acres while, in the United States in North America, 20% of the working population cultivate 360,000,000 acres. Conditions in India are not very dif-

ferent from those in China. In 1945, some 5 million died of famine, and 500,000 of cholera. The increase in population of these two countries is calculated at about 1% a year, or 10 million a year at the present time. Extremes in birth rates are represented by Austria with 12.8 in 1937, and by Costa Rica with 54.3 in 1947. The Central and South American birth rate was 43 per thousand population in 1930, which was 2 to 3 times that of North America. If the public health measures which have produced the tremendous population increases in Japan, Indonesia and Puerto Rico could suddenly be applied to the entire population of more than 1,000,000,000 in India, China and South America, it would be necessary tremendously to accelerate application of presently known methods of production and distribution of food, in order to forestall catastrophe.

Under the World Health Organization of the United Nations, a world wide campaign of disease prevention is taking shape. Already it has very efficiently limited to Egypt a cholera epidemic which might have become world wide. Its campaign to prevent malaria, tuberculosis and infant mortality is yielding splendid results. President Truman's Point 4 Program will enable technically underdeveloped countries to improve their efforts in the field of health.

The trend toward urbanization and industrialization of populations has reduced the economic value of large families. Industrialization has supplied the machinery and power to increase man's capacity to produce food, and it also has generated those psychologic forces which have steadily reduced birth rates. As a result of the reduction in the size of families, the many countries of North America and Western Europe have entered a third stage in population trends, in which low death rates are being matched by low birth rates. It is of interest, however, that even in these areas there has been a great increase in birth rates in the last 10 years.The matching of rates, therefore, is less perfect than it was and population is increasing.

That the population of a country can remain practically constant by balancing its births and deaths is demonstrated by Ireland. In 1845 its population had reached 8,295,000 following introduction of the potato, which provided an abundant food supply. Several years later, Ireland had a series of failures in the potato crop and, as a result, more than 1,000,000 people died of starvation and another 1,000,000 emigrated. By means of celibacy and few and late marriages, the population was reduced so that, in 1938, it was about 3,000,000, slightly less than in 1926 and 5% less than in 1911. In 1939 the birth rate was 18.9 per 1,000, one of the low rates for Europe, and the death rate was 13.8 per 1,000 which, with emigration, resulted in a slight loss of population.

The comparatively recent experience of three other countries comes to mind. As early as the end of the last century, France was making every effort to reduce her high infant mortality, because the lowered birth rate had slowed her rate of increase in population until it was far below that of surrounding countries. The work of Pierre Budin, in 1892, contributed greatly to diminishing infant mortality. His Consultation des Nourisson in Paris, in slightly modified form, has served as the model for the well baby clinic of today. With a birth rate of 20 per 1,000, the population can go up, down, or remain stationary, depending on death rates. In England and Sweden, the birth rate in the nineteen thirties fell as low as 14 per 1,000, but owing to the increased life span there was no decrease in population, with a marked increase in the older age groups.

If there should occur a decrease in the present high birth rate in rural communities in countries which follow the western European pattern, and among the underprivileged

in the urban centers, where now many more than their share of children is being produced, there would be an over-all sharp decline in births unless, at the same time, a definite effort should be made to increase the birth rate of the eugenically more desirable elements of society.

That this third stage in population trends applies to only a small portion of the world population is evident from the increase in the population of the world of roughly 20,000,000 in a year.

It thus becomes evident that, with this rapid increase in population, there must come a time when the food supply in the world will no longer feed, even inadequately, the population of the world. After thorough study of the food situation of the world the Food and Agriculture Organization of the United Nations stated that, on a global basis, the per capita ration is smaller today than it was 10 years ago. This means that the increase in population of 200,000,000 has outstripped the production and distribution of food that is necessary to match the increase. The Food and Agriculture Organization stated, further, that more than two thirds of the people of the world at present do not get enough to eat. Most of the people of India get less than 1,750 calories a day, and most of those of El Salvador, less than 1,600. In addition, there are many specific food deficiencies: for instance, those attributable to lack of protein in the diet, aside from vitamin deficiencies such as pellagra. It is not only that the food must be raised by farmers and ranchers, but the money must be made available to purchase it and transportation must be arranged to bring the food to the inadequately fed.

The theme that increase in population might outstrip the possible food supply was elaborated by Malthus many years ago. He was contradicted by Henry George who found adherents in those who think that there is no limit to the possibilities of production of food in the world. More intense fertilization on farms; irrigation; development of more rapidly ripening grains for planting in far northern and southern countries; increase in yields by the use of new hybrids; production of vegetable oil in the tropics, prevention of loss by rodents, insects and parasitic diseases; increased storage facilities; use of yeasts grown on sugar made from wood to supply protein food—all these, some believe, will keep food production greater than the needs of the rapidly growing population. There are those, on the other hand, who think that there is a limit to the amount of food that can be produced even with the best of farming and the use of all available land, as well as employment of other means of production of food. Such persons believe that the supply ultimately will not be able to meet the demands of an adequate diet for a world population that is increasing at the rate of 20,000,000 a year.

Sooner or later, unless the availability of food is augmented, the rapidly increasing population must precipitate a food crisis of world proportions, unless the crisis is met by increase in the mortality rate, or decrease in the birth rate, or both. It is unthinkable that man, and particularly physicians, will accept reversion to excessive death rates from diseases now controlled, or refrain from still further working to prevent disease and death by all possible measures. We pediatricians in particular have made it our work to prevent disease of children, and we have gone even further in making it our duty "to develop in children those mental, spiritual, and emotional qualities that make for happy childhood and growth to responsible citizenship," as was so well brought out in the recent Mid-Century White House Conference on Children and Youth. "Man does not live by bread alone." His emotional and spiritual life also must be satisfied.

If mortality rates must not be allowed to increase—and they must not increase—and if, at the same time, the increase in population must be checked, then birth rates must be reduced. As long as nationalism runs riot as it did in Germany under Hitler, in Italy under Mussolini, and as it does in the Union of Soviet Socialist Republics under the present leadership, reduction of population is impossible. "Women have been relegated to the status of producers of babies for service to an all powerful state."

In spite of many local handicaps, the problem must be met by each state individually. Each needs a program that will balance its birth and death rates within its ability to feed, clothe and house its people. Provision must be made, also, for those amenities of life which are considered necessary at this stage of human development. These national population programs must be integrated into a world population program.

Accordingly, it is encouraging that population trends are receiving national as well as international attention. The Executive Board of the World Health Organization, realizing the importance of population trends, has requested the World Health Organization to continue its study of population problems. The board has urged particular attention to those aspects of the problem that pertain to health, including measures for control of increases in population.

A recently drafted government program for India calls for the development of measures to limit the size of families. In January, 1949, Japan enacted a law with the same purpose. The Rockefeller Foundation, in its study of population and public health in the Far East, concluded that an effective and complete health organization should assist in replacing the wasteful system of high fertility and high mortality by an efficient system of low fertility and low mortality. Emphasis was placed on healthy children rather than many children. The Rockefeller Foundation, as well as other agencies, emphasize that the control of fertility in the rural populations of the world offers the greatest opportunity for effective work. The development of effective means of controlling the size of families is essential to the success of this program.

There was a time when the prevention of disease was considered to be interfering with the work of God; it no longer is so considered. If human interference with the natural course of events in increasing the span of life is justifiable, is it not equally justifiable to stop excessive fertility? We pediatricians, who are in no small measure responsible for the greater number of children who reach maturity, should help to develop a plan by which the birth and death rates can be so balanced that the countries of the world will eventually be able to make available to their children of this and future generations the best in life.

SPECIAL ARTICLE

SOME ASPECTS OF AUSTRALIAN PEDIATRICS

By LORIMER DODS, M.V.O., M.D., F.R.A.C.P., D.C.H.
Sydney, Australia

MR. PRESIDENT, Ladies and Gentlemen: May I begin by telling you how very much I appreciate the honor of being invited to address your society and by thanking you for the compliment to Australian pediatrics which this invitation implies. Your President, Dr. Hodes, has just referred to my maternal American genes and I hope that the presence of these chromosomes may help in some little way to improve my status as an amateur ambassador of Australian pediatrics in this country. Just in case your President's other kind remarks have given you the wrong impression, I feel that I should begin by offering you some sort of explanation of my present professorial act which is a new and very shaky one.

During the past 10 or 15 years, a form of animal life, well-known in your country for at least half a century, has appeared with increasing frequency in various universities of the British Isles, a new species of "homo medicus"—in other words, the professional pediatric pedagogue complete with chalk and blackboard. For the past two years I have had the honor and the rather doubtful pleasure of being the first example of this new form of animal life to appear in the Australian pediatric jungle. As most of you know, pediatrics is a very young and Cinderella-like specialty in our country. A little more than 25 years ago when I first faced the general public as a would-be physician it was regarded as impossible for a young man to earn an adequate living as a pediatrician, and as a result, almost half of my professional life has been spent in general practice. So now I stand here as the old family doctor very thinly disguised as an academician, rather out of place in this gathering of modern pediatric priests and prophets, but extremely proud to be asked to address you all. A wise old Frenchman once defined the essential requirements of a family physician as "un peu de savoir, beaucoup de savoir-faire and assez de faire savoir." Like many other family physicians, I have relied to a large extent on this essential trinity but I must admit that I have also been helped by another factor which is difficult to define to an audience such as this because it represents a quality which must be extremely remote from your own life and work, and because it lacks an appropriate label. The Greeks, who had a label for most things, were very much aware of this strange factor which they called "pseudologia fantastica" and I understand that a younger and more outspoken generation on this side of the Atlantic has associated it with the name of Taurus Magnus.

And now, after all this explanation and apology I would like to say something about a few aspects of Australian pediatrics which I hope may be of some interest to you.

Firstly your own subject, the problem of pediatric research. I think that to most of us this word "research" suggests the laboratory, the long white coat and the peace and quiet of the cloisters. For various reasons, extraordinarily little pediatric research of this type has been achieved in Australia and most of the little original work which we have to report

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has been carried out by men or women in the course of their everyday medical practice.

Charles Clubbe's work on intussusception which belongs to the turn of the last century represents a typical example of this "bread-and-butter" type of clinical investigation. Dr. Clubbe, a busy general practitioner-surgeon who was appointed to the visiting staff of Sydney's newly formed Children's Hospital in the early 1880's, carefully studied and recorded in detail 270 cases of intussusception treated by him during more than 25 years of private and hospital practice and in 1906 published a book on the diagnosis and treatment of this condition which achieved a wide sale in Australia. Clubbe's work and teaching and his book were responsible for instilling into the mind of the Australian general practitioner the clinical picture of intussusception in its very early stages and played a significant part in the tremendous reduction in the mortality rate of this disorder which fell from more than 90% to approximately 12% during his 40 years of active practice in Sydney. At the present time we are proud of the fact that more than 75% of infants diagnosed as suffering from intussusception are admitted to our Children's Hospital less than 24 hours after the onset of the disorder and I feel that this satisfactory state of affairs is probably directly related to the crusade for early diagnosis initiated by Clubbe more than 50 years ago. About 30 years ago one of Clubbe's junior colleagues, P. L. Hipsley—another busy general practitioner-surgeon—published details of his method of reducing intussusception by hydrostatic pressure. The idea was not new as Hirschsprung used water enemas for this purpose in 1870 and Clubbe had used injections of warm olive oil with some success during the early years of the twentieth century, but Hipsley's report of his first hundred cases treated by this method was of special significance as he achieved the amazingly low mortality of 5% at a time when the mortality in many centers was about 20% or more.

Although Selter of Germany published a report of eight children suffering from a disease similar to Pink disease in the year 1903, his clinical description was a very fragmentary one and I think that it is reasonable to say that the first complete and satisfactory report of the clinical picture of Pink disease came from Swift of Adelaide in 1914 —an excellent clinical description which was based on 66 cases observed by Swift during the course of more than 20 years of busy medical practice in the small city of Adelaide. Unfortunately we in Australia have added very little to our knowledge of this disease during the 40 years which have followed Swift's original observations and we have obviously left undone those things we ought to have done in this field, but I have hopes that Warkany's intriguing work on the probable significance of mercury as an aetiological agent may help to jolt us out of our present clinical climacteric and that we may have more to report about this disease and its aetiology in the near future.

As Pink disease is not notifiable we have no real evidence about its incidence in our community, but like some of my colleagues, I suffer from the rather fixed impression that small epidemics of this disease occur from time to time in country towns or city suburbs or even in a localized section of a suburb. Sir James Spence once told me, possibly with his silver tongue in his cheek, that an epidemic of this disease could be precipitated at will, in a given area, by means of an enthusiastic postgraduate lecture, but lacking his evangelical ability we have so far failed to induce an epidemic by this means.

We have been interested for many years in the fact that repeated cases of Pink disease may occur in one family and at present I know of 6 families in which 2 children have been affected, and 2 other families in which 3 children have suffered from this disorder. In

one of these very unfortunate families, 3 successive infants suffered from Pink disease during a total period of about 5 years, the second infant dying from this disease before the birth of the third child who developed the malady at one year of age. In each family there has been an interval of from 1 to 3 years, or even longer, between individual cases, an interval which may possibly be explained by the rather constant age of onset of this disease which apparently has to wait patiently until another child is born and reaches an appropriate age before it can strike again.

In our experience of the sequelae of this disease, bronchiectasis has been by far the greatest hazard and at the present time Pink disease stands third on the list of diseases which we assume to be responsible for initiating bronchiectasis amongst Sydney children—a very close third to pertussis which occupies second place on this list. Speaking of bronchiectasis, I would like to mention the very low masculinity rate of this disease amongst children in Sydney, the proportion of females to males attending our Children's Hospital bronchiectasis clinic being approximately 2 females to 1 male. We feel that this marked preponderance of females may be partially explained by the surprisingly low masculinity rate of pertussis amongst Australian infants—a rate which stands in sharp contrast to the very high masculinity of other infections during early infancy in our country.

Dr. May who is sitting just over here on my right has been talking to me this evening about the significance of the pioneering work on the subject of congenital pancreatic fibrosis carried out by Margaret Harper of Sydney during the 1920s, and he feels with me that her first paper on this subject with its excellent description of the clinical and the postmortem features of a small group of cases which she recognized in her own practice probably represented the first satisfactory and logical description of this disorder to appear in the English language.

We are naturally extremely proud of Norman Gregg's dramatic incrimination of maternal rubella during pregnancy as a cause of certain congenital malformations. This outstanding discovery was achieved by a man of 50 in the midst of the stress and turmoil of an extremely busy professional life and stands as an excellent example of the type of valuable original work which may be carried out in the course of everyday medical practice.

At the risk of gilding the lily and perhaps boring some of you I would like to say something about the man himself, for many reasons, but more particularly because Norman Gregg represents an excellent clinical example of that very rare syndrome, the "all-rounder"—a brilliant scholar who collected a long series of special academic honours and prizes both at school and at the University, an outstanding all round athlete who represented his university and his state at cricket, tennis and baseball and even managed to play football for the Australian Army in 1918, an extraordinarily successful and busy professional life, a great influence as a teacher in our medical school and with all these things, a genuine and natural modesty which has made him a very popular member of our small medical world.

Gregg's original work and its amplification by Swann and others has stimulated some of us to make an attack on a few of the more obvious problems of prenatal pediatrics and we are hoping by means of "prospective studies" to come to some conclusion about the possible significance of virus infections, uterine hemorrhages, excessive vomiting and other disturbances occurring during the early months of pregnancy as factors in the aetiology

of stillbirths and congenital malformations. In this respect we are also interested in such condition as hydramnios and oligohydramnios (if you are willing to accept such a word and admit such a condition!), and the age of the parents—or rather, the age of the mother, as I am sure you will agree with me that various human frailties would make the age of the father a dangerous subject for statistical study.

Speaking of paternity, I recently found an early medical study about Hippocrates which may please you. Apparently Hippocrates who in his great wisdom had officially denied the "maternal-impression" theory of congenital malformations, cheerfully saved the honour of a fair and beautiful princess accused of adultery with a Negro, by pointing out that a large painting of a black slave on the wall of her bed chamber was responsible for the unfortunate pigmentation of her infant's skin—a story which may help to illustrate the Hippocratic sense of *noblesse oblige* and may even add some further support to that age-old aphorism that we should never underestimate the power of a woman.

And now to return for a moment to the subject of maternal rubella, I would like to tell you about some epidemics of congenital deafness which occurred in Australia and New Zealand many years before Gregg's discovery and which have been studied and verified by Oliver Lancaster, our lecturer in medical statistics. By reviewing the dates of birth of all deaf persons admitted to institutions for the deaf and dumb in Australia, Lancaster established the fact there were epidemics of congenital deafness in Australia in 1899, 1916, 1924 and 1938, and that each epidemic of births of the deaf was preceded by an epidemic of rubella during the previous year. Lancaster also found that similar epidemics occurred in New Zealand in 1898, 1900 and 1938. I feel that this significant evidence may help to illustrate the unfortunate hiatus which frequently exists between statistical and clinical medicine, for if the clinician had appreciated and interpreted these figures, maternal rubella as a cause of deafness might have beeen recognized more than 30 years before it was.

These epidemics of deafness naturally suggested to us that studies of the possible epidemicity of some of the commoner congenital malformations might be helpful in the elucidation of their aetiology, but so far we have been unable to establish the epidemicity of any congenital defect, apart from deafness.

It may interest you to know that Norman Gregg's first knowledge that deafness may follow maternal rubella during pregnancy came from that excellent clinical observer—the mother. Gregg's original paper which emphasized such defects as cataracts and congenital heart disease but did not include any statement about deafness was given some publicity in Sydney's popular press on a Monday morning and he tells me that before lunch on that day two mothers had telephoned to say that they had suffered from rubella during the early stages of their pregnancies and that their children were deaf but were not suffering from any other of the defects defined by him.

It was another clinical observation by a mother which led to the recognition of the factors responsible for the very high incidence of lead poisoning amongst Queensland children during the latter years of the 19th century. In the late 1880s medical practitioners in the relatively new settlement around Brisbane, which lies on about the 29th parallel, became aware of a new and frightening disorder which was surprisingly common in this area and which they recognized as a form of lead poisoning. In 1892 two Brisbane practitioners published an excellent clinical account of the "paralytic form" of this disorder of childhood, emphasized the fact that lead was responsible, but admitted they could

not establish the source of this poison. A few years after the publication of their paper a mother of a large family remarked to one of these men that the only two children in her family to develop lead poison were the two "nail biters." It was this illuminating chance remark—in its minor way, almost as significant a remark as that of the dairy maid to Jenner—which pointed to the source of the lead and saved the life and health of innumerable Australian children. The answer was now obvious—the houses of this new settlement were wooden ones with wide verandas and the paint on these verandas and their railings quickly became dry and powdery in the hot Queensland sun. During the summer months young children spent most of their days playing on these verandas and the dried paint reached their mouths as a powder on their hands, or in the even more potent form of rain drops collected by running their small fingers along the under surface of a wet veranda railing.

Once again, it was the mothers themselves who by repeated and persistent questions about a possible relationship between recent immunizing injections and their infants' paralytic forms of poliomyelitis stimulated a young Melbourne public health officer, named McCloskey, to investigate this problem. Three years ago, in May 1949, McCloskey submitted his first written report on this subject to the health department of the state of Victoria—a report which naturally provoked some opposition and criticism. Despite this opposition, McCloskey continued his work and early in 1950 his paper incriminating injections of pertussis vaccine as significant factors in the precipitation and localization of the paralysis of poliomyelitis was accepted by the high priests of statistics both in Australia and abroad.

During the recent Australian epidemic of poliomyelitis a member of our department—F. N. Street—attempted to assess the possible significance of various "noxious influences" operating during a period of 30 days before the onset of poliomyelitis. Although this study failed to produce any new evidence of importance, it confirmed McCloskey's statements about pertussis vaccine, suggested that the operations of laparotomy and appendectomy seemed to play some part in the precipitation and localization of the paralysis of poliomyelitis and added further emphasis to the significant part played by undue fatigue and excessive muscular exercise during the incubation period and the early stages of this disease.

During the latter stages of this epidemic, another member of our department, David Dey, carried out a clinical review of approximately 700 children who had been recommended for tonsillectomy by experienced observers who were members of the visiting staff of Sydney's Children's Hospital. As a result of this survey of approximately 700 children whose operations had been deferred because of the hazard of poliomyelitis, it was concluded that 37% of these children did not require tonsillectomy when re-examined and reassessed 18 months or more after their original examination. Like many other observers of this problem, Dey has also collected some evidence which suggests a possible relationship between the incidence of tonsillectomy and "the jingling of the guineas," for he found that about 49% of a series of children attending free public schools in Sydney had lost their tonsils, while more than 72% of a similar series of children attending private schools in the same city had lost theirs.

During the early months of 1951 while certain areas of Australia were still suffering from epidemics of poliomyelitis, a severe form of encephalitis associated with a very high mortality, suddenly spread among families living along the valley of a large river in

Victoria known as the Murray; more than half of the sufferers were infants and children less than 12 years of age, and the mortality was at its highest in this age group. Some of you may have heard all the details of this epidemic of "Murray Valley encephalitis" from Sir MacFarlane Burnet during his recent visit to this country, but I feel that the story is well worth repeating. By a strange coincidence, this frightening epidemic occurred in a district where the rabbit virus disease, myxomatosis, had recently been introduced in the hope of destroying some of Australia's vast armies of rabbits. Before introducing myxomatosis into Australia, Professor Burnet and his associates had made it very clear to the public that this rabbit virus disease would not affect human beings, but this original assurance and its emphatic repetition failed to stop certain sections of our popular press from suggesting to a naturally frightened public that this severe outbreak of human encephalitis might be caused by myxomatosis. The successful investigation of this epidemic by Professor Burnet and his staff proceeded very quickly—the virus which is similar in many ways to that of Japanese B encephalitis was isolated from an early fatal case, a significant antibody titre was demonstrated in the sera of a small percentage of unaffected humans and in a certain percentage of horses and dogs, and evidence was produced to suggest that young water bird nestlings represented the primary reservoir, that a mosquito was the vector and that horses and dogs may have played a part as intermediate hosts. Just to round off this successful investigation, myxoma-complement-fixing antigen produced negative results with all sera tested from humans, horses, dogs and birds, and even the popular press was satisfied!

This talk of rabbits may provide me with a flimsy excuse for saying something about pediatrics and other medical problems in our remote "out-back" areas.

Recently I had the good fortune to be sent by our commonwealth government on a most interesting pediatric consultation and inspection tour of the "out-back" areas of central and northern Australia, visiting doctors and small cottage hospitals in remote areas, small nursing homes in even more remote areas, mission stations and aboriginal settlements. At each home or settlement, pediatric and other medical problems had been collected and I tried, with very little success, to answer some of the innumerable practical problems which these isolated doctors, nurses and missionaries are forced to deal with every day of their lives.

Most of the settlements which I visited lay between 20° and 10° south latitude—an area comparable in latitude to that of southern Brazil. A significant proportion of Australia's 50,000 aboriginals live in this section of Australia, many of them working with the white man, but some still living in their primitive state in the surrounding bush or desert country, moving from water hole to water hole, making their own fire and hunting their own food.

The three outstanding medical problems amongst the aboriginal children in this area are tuberculosis, leprosy and hookworm and the control of such conditions amongst a very primitive people living in extraordinarily close contact in their tiny bush and bark "humpies" represents a very difficult problem. As a simple example of the sort of problem which faces the would-be hygienist, I found that one mission station had recently constructed a series of galvanized iron latrines with cement floors and had optimistically tried to persuade the natives to use them. The more go-ahead natives immediately sensed the new housing opportunity, moved their wives and children into these modern architectural structures and cheerfully made a crowded home of each latrine.

At one mission station I was surprised to find a group of three children in one family and a cousin all suffering from an unusual form of genetic intersexuality and to learn that two adults related to these children also presented evidence of the same condition. The two adults concerned very wisely "went bush" as soon as the suggestion of clinical examination reached them, but I have hopes that this whole family will be investigated and reported later. The old priest in charge of this mission station kindly offered to provide a family tree of this group for me, but pointed out with a cheerful smile that a multiplicity of fathers would add some confusion to this document. This question of aboriginal family trees is also complicated by the fact that many of our very primitive aborginal tribes do not accept the fact that sexual intercourse has anything to do with pregnancy. Apparently amongst these more primitive tribes, pregnancy is not accepted until the first movements are felt and this is regarded as the moment at which the "child spirit" responsible for pregnancy is supposed to have entered the woman's body. As an extension of this form of reasoning, it is apparently very difficult to persuade an aboriginal woman from one of these primitive tribes that a very premature infant is merely an undeveloped human being; this progeny is usually regarded as that of an animal spirit which has entered the woman's body by mistake—a very simple and satisfactory rationalization of this form of fetal wastage.

Confinements are usually conducted in a small cleared area of scrub near the camp, the ground being raked clear of sticks and leaves and often covered with wood ashes. The mother squats on her heels with her thighs separated and is supported by a woman attendant—often her mother-in-law!—who squats behind her and grasps her around the abdomen. The labor is usually short and easy. The infant is born on to the ground, the cord divided with a sharp stone or piece of shell and the infant sprinkled with some fine wood ashes. The mother rests for most of the next 24 hours and returns to her usual duties with the tribe on the third day.

Breast feeding usually continues until a child is 3 or 4 or even 5 years of age. I understand from observers that the mother's older infant of perhaps 2 or 3 years of age who has been kept away from his mother during her confinement occasionally provides a sudden adequate stimulus for the third stage of labor, by rushing in to get his share of the breast milk, as soon as possible after the end of the second stage.

Amongst some of the very primitive tribes, twins are regarded as unnatural and the weaker or smaller one is usually killed immediately by the simple process of filling its mouth with sand, a most efficient form of therapy probably instituted by the wise old tribal medicine men because of the bitter struggle for food which many of these tribes faced. In view of this ritual, I was very surprised to learn that most aboriginals accept and do not destroy the malformed infant.

Those of you who were in Australia during the war may have seen something of the "flying-doctor service" which was established by a Presbyterian missionary doctor, John Flynn, about 20 years ago in an attempt to provide some sort of medical aid for the people living in the more remote areas of our "out-back" country. Beginning with 2 or 3 very small nursing homes, each staffed by two nurses and each communicating with Australia's one and only flying doctor by means of a stationary bicycle-pedal wireless, this service has developed rapidly until it now consists of a series of flying doctors, each stationed at a small base hospital equipped with a powerful wireless transmitter-receiver. Each of these flying-doctor bases is in the center of a circular area which has a radius of about 500

miles and scattered throughout this circle are a series of "plain-speech" transmitters and receivers installed in cattle station homesteads and in other "out-back" dwellings, and near each of the centers there is a home-made landing ground. Medical messages are received and answered at fixed times during the day; many of these are answered by advice over the air and by directions about drugs which are available in specially numbered bottles in medical first-aid chests issued by the flying-doctor service to homesteads. A certain number of calls are answered by the flying sister going out to give first aid and to bring the patient in to the hospital and in other specially selected cases the doctor himself flies to the patient in an attempt to do something on the spot. In addition to this type of urgent service the flying doctor now conducts clinics 2 or 3 times a year in various centers within his circle, carrying out a routine examination of all children brought to these centers and arranging for such treatment as may be indicated.

Sitting at a flying-doctor base in the center of Australia, listening to the urgent medical calls, I was amused to hear a man's voice saying, "I don't now whether you would call this an *urgent medical* call, but it is *certainly urgent* . . . one of my stockmen has gone off his rocker and is chasing his mate with an axe." I was most impressed to listen to these relatively young doctors sorting out a confused clinical story and giving immediate sound practical advice over the air. I was even more impressed to go with one of them and see him deal with a medical emergency. To fly with one of these men to see an almost moribund, dehydrated infant in a three room shack more than two hundred miles from any settlement, to watch the immediate resuscitation in the home and to observe the infant's recovery later at a small base hospital is to sense something of that feeling of genuine service and gratitude which has warmed the hearts and minds of generations of "out-back" doctors in many countries.

Finally, I would like to say just a few words about the question of teaching. Unfortunately our medical school in Sydney has been grossly overcrowded during recent years and we have been faced with the very difficult problem of trying to teach something about pediatrics to more than three hundred students each year. The knowledge that at least 75% of these men and women will spend most or all of their lives in general practice, and the realization that the general practitioner is responsible for the great bulk of pediatric practice in our country, may help to emphasize the significance of our pediatric teaching problem.

At first thought, it might sound relatively simple to give the student a single quick infusion of pediatrics under some form of positive pressure, but I am convinced that this single infusion is not enough and that positive-pressure methods are dangerous both for the student and the teacher. I think that you will agree with me that if the general practitioner is to be of real value as a pediatrician in his suburban or his "out-back" country practice, he must have sufficient genuine interest in this subject to maintain some sort of self-administered continuous or intermittent infusion of modern pediatric knowledge. I consider that it is our first and foremost duty as teachers of pediatrics to promote and stimulate this interest—our special responsibility to try by every means possible to create at this impressionable, undergraduate age a genuine and lasting interest in this subject.

Some hard-headed realist once defined a formal didactic lecture as a method of transferring facts from the lecturer's notes to the student's notebook without those facts passing through either mind. I realize there are many exceptions to this very painful defi-

nition and that the didactic lecture has its place as an occasional instrument of teaching, but I feel that we should protect the student as much as possible from unnecessary lectures and sermons, that we should come down from the pulpit and talk with the student rather than at him, travel some of the clinical road with him, ask for and face his questions and share with him the responsibility of finding some of the answers.

Following the teachings of Sir James Spence, we have also been doing what we can to help the student to visualize the child against the natural background of the family and the home instead of the artificial decor of a hospital ward or clinic, trying to help him to appreciate the possibilities and limitations and the everyday activities of his own office and of the little local hospital on the corner of the street and trying to help him to appreciate something of the intimate human relationships involved in many pediatric problems.

And now, after this breathless sermon which seems to have led me some way from the straight pediatric path, I feel sure that you can all appreciate the full significance of my original warning about Taurus.

NEWS AND ANNOUNCEMENTS

POSTGRADUATE COURSE IN PEDIATRIC ENDOCRINOLOGY AND METABOLISM

A Pediatric Postgraduate Endocrinology and Metabolism course will be held at the Burnham Memorial Hospital for Children, Massachusetts General Hospital, Boston, under the direction of Dr. Nathan B. Talbot and associates, Oct. 6 through Oct. 11, 1952, daily from 9:00 a.m. to 4:30 p.m. For further details, write Courses for Graduates, Harvard Medical School, 25 Shattuck St., Boston.

* * *

ANNOUNCEMENT OF PEDIATRIC RESIDENCY FELLOWSHIPS

Through the generosity of Mr. D. Mead Johnson and Mead Johnson and Company, the American Academy of Pediatrics is pleased to announce that 8 fellowships for pediatric residents will be available for a period of one year, beginning Jan. 1, 1953. Each recipient will receive $1,000. These awards will be made annually.

Criteria for the awards will consist of the following: (1) a letter from the Chief of Service indicating that the proposed individual has completed, or will have completed by Jan. 1, 1953, one year of pediatric training credited by the American Board of Pediatrics; that the resident has performed his work ably; and that there is real need for financial assistance; (2) a letter from the resident requesting the fellowship stating that he intends to enter pediatric private practice at the conclusion of his second year of training. Consideration will be given to geographic spread of appointments, so that all sections of the country will be represented, and preference will be exhibited for well-qualified but smaller training centers who perhaps have fewer resources for assisting residents in training than do some of the larger centers. Geographically, the awards will be limited to 7 to the United States and one to Canada. Note that research interests and accomplishments and desire to enter academic pediatrics are not criteria for the awards.

Members of the Committee on Residency Fellowships of the American Academy of Pediatrics who will make final decision on the appointments are: Dr. James G. Hughes, Chairman, Dr. Henry G. Poncher, and Dr. Robert B. Lawson.

Those interested in applying may correspond with Dr. James G. Hughes, Le Bonheur Children's Hospital, Memphis 5, and will receive application forms.

The deadline for receipt of these applications will be Oct. 1, 1952.

* * *

The Jacobi Fund of the Section on Pediatrics of the AMA received $1696 from 282 contributors according to the report made at the June meeting in Chicago by Hugh L. Dwyer, M.D., Custodian.

Net income from investments was $188.76. Expense and distribution to essayists was $731.80. Trust value May 30, 1952, was $6890.04.

* * *

The following diplomates have been certified by the American Board of Pediatrics, Inc.:

San Francisco—June 27, 28 and 29, 1952

Baecker, Marvin Philip, 4644 Blackthorne, Long Beach, Calif.
Ball, James I., 500 Middlefield Rd., Palo Alto, Calif.
Bierman, C. Warren, Madigan Army Hospital, Tacoma
Bray, Patrick Francis, 224 S. 12th East, Salt Lake City
Brown, Albert A., c/o Stromberg, 1556 S. Rexford Dr., Los Angeles
Carr, John Howard, 13 Sirard Lane, San Rafael, Calif.
Carroll, Herbert B., 5623 California Ave., Seattle
Child, Stanley Roberts, 1204 E. S. Temple St., Salt Lake City
Coleman, Harold S., 6317 Wilshire Blvd., Los Angeles
Conrad, John P., Jr., 716 E. Olive, Fresno, Calif.
Crehan, Elmer Leo, 2206 W. Third St., Los Angeles

Dana, George Winchester, The Portland Clinic, 1216 S. W. Yamhill St., Portland, Ore.
DeKruif, Alice D., 6218 Crown Ave., Oakland, Calif.
DeVito, Alfred Thomas, 1116 E. Third St., Moscow, Ida.
Dicken, Dorothy M., 105 Soquel Ave., Santa Cruz, Calif.
Dittmann, Barbara Edith, 1358 Miramonte Court, Berkeley, Calif.
Donaghe, Roy Wallace, 605 Gore Blvd., Lawton, Okla.
Dowell, Margaret, 1246 Center St., Salem, Ore.
Ely, Robert Stewart, Salt Lake General Hospital, Salt Lake City
Fisher, Ralph M., 1209 Eaton Ave., San Carlos, Calif.
Friend, William K., 2320 Riverside Dr., Santa Ana, Calif.
Goorman, Jean R., 5255 De Longpre Ave., Los Angeles
Greig, Jack Leland, 2718 Garber St., Berkeley, Calif.
Gross, Ruth T., 2301 Pacific Ave., San Francisco
Grossman, Moses, 2935 Irving St., San Francisco
Gudbrandsson, Bjorn, c/o Iceland Legation, Washington, D.C.
Harris, Francis Marion, Jr., Capt., 4050th A.S.U., U.S. Army Hospital, Ft. Sill, Okla.
Hartenstein, Hans, 1st Lt. (MC) 01921164, Ryukyus Army Hosp., 8114th A.U., APO 719, c/o PM, San Francisco
Haumeder, Robert R., 273 Douglas Lane, Walnut Creek, Calif.
Henderson, Oliver Morton, 50 Selfridge St., Vallejo, Calif.
Herzon, Herbert, 515 School St., Pittsburgh, Calif.
Hodes, Abram, 1963 Pershing St., San Bernardino, Calif.
Jennison, Maurice Harry, Lt. (jg) MC USNR, 902 Bougainville, Oceanside, Calif.
Jensen, Adrian Richard, Peacy Manor Apts., Rt. #1, Waukegan, Ill.
Kaufman, Harry, 3959 Laurel Canyon, Studio City, Calif.
Kelley, Vincent Charles, Dept. of Ped., Univ. of Utah, Salt Lake City
Kempe, C. Henry, Dept. of Ped., Univ. of Calif. Hospital, San Francisco
Kennedy, Walter James, Jr., 5102 Bitter Root Way, R. #3, Yakima, Wash.
Kirchhoff, Clyde August, 72 Eugenia Dr., Ventura, Calif.
Klitsner, Irving Neil, 130 N. La Cienega, Los Angeles
Krempels, Geza Joseph, 529 E. 10th St., Long Beach, Calif.
Lambert, Tempe Chester, 777 Bryant St., Palo Alto
Lawler, Harry James, 1131 N. 29th St., Billings, Mont.
Lembert, Glenn E., 1104½ Main St., Vancouver, Wash.
Levy, Bertha Marion, 1200 N. Walker, Oklahoma City
McMain, William A., Jr., 60 S. Fourth East, Salt Lake City
Miller, Lewis Richard, Peninsula Clinic, 500 Arguello St., Redwood City, Calif.
Mitchell, John Roy, Box "O", Ancon, Panama Canal Zone
Montgomery, Theodore Ashton, 3115 W. 76th St., Los Angeles
Moss, Edward Mitchell, Lt. (MC) USNR, 4152 Randolph St., San Diego, Calif.
Mulloy, Mary, 4614 Sunset Blvd., Los Angeles
Nelson, Thomas Lothian, P.O. Box 1488, Eldridge, Calif.
Palmer, Robert Hall, 23 Baldwin Ave., San Mateo, Calif.
Peat, Alexander Cranston, Major, 39th Med. Group, APO 942, c/o PM, Seattle
Plumb, Hugh J., Jr., 420 Jasmine, Corona Del Mar, Calif.
Pulido, Venustiano, 3959 Laurel Canyon Blvd., Studio City, Calif.
Reuben, Ronald, 6317 Wilshire Blvd., Los Angeles
Rice, Don Brooks, 204 Boivin Bldg., 110 N. Sixth St., Klamath Falls, Ore.
Robinson, William Taylor, Woodland Clinic, Woodland, Calif.
Schafer, William Boulware, 3907 Ocean View Blvd., Montrose, Calif.
Schwartz, Marvyn Sherman, 1590 N. Van Neso, Fresno, Calif.
Shaffer, Harry Daniel, 805 Prairie Rd., Colorado Springs
Smith, Robin, 104 N. Commercial St., Neenah, Wis.
Stool, Joseph A., 3718 Travis, Houston
Sturgeon, Phillip, 4614 Sunset Blvd., Los Angeles

Sutherland, Donald Arthur, 11326 Second Ave., N. W., Seattle
Sutow, Wataru Walter, Capt. MC 0-1921810, Atomic Bomb Casualty Commission, APO 182, c/o PM, San Francisco
Tepper, Warren Roswell, 1322 Penn St., Salt Lake City
Thomas, Lloyd Allen, Capt., Qtrs. T 315 A, Camp Stoneman, Calif.
Tolins, Peter S., 328 Maple St., San Diego
Tucker, James Louis, 120 Northgate Plaza, Seattle
Tyson, Robert Glenn, Permanente Hospital, Vallejo, Calif.
Vracin, Daniel John, 10727 S. Paramount Blvd., Downey, Calif.
Whittinghill, John A., 2814 Ninth Ave., North, Billings, Mont.
Wood, John W., Atomic Bomb Casualty Commission, APO 182, c/o PM, San Francisco
Woodcock, Herbert M., 1568 Paulsen Bldg., Spokane, Wash.

The following oral examinations are announced: Chicago—Oct. 24, 25 and 26, 1952; Boston, Dec. 5, 6 and 7, 1952.

BOOK REVIEWS

THE OTHER CHILD, Richard S. Lewis with Alfred A. Straus and Laura E. Lehtinen, New York, Grune & Stratton, 1951, $2.50, 108 pp.

Strauss and Lehtinen in a book published in 1947 described their observations of the behavior and psychologic deviations of what they called "brain-injured" children. By this term they referred to children showing abnormal behavior and learning patterns involving disturbances in perception, thinking (conception), language and emotional states, presumably the result of prenatal, natal or postnatal cerebral injuries or developmental interferences. The present book *The Other Child* was written by R. S. Lewis, a parent of one of these children who was selected by Strauss and Lehtinen because he was a professional writer and might best express in layman terms what they had attempted professionally in their 1947 book. The "Other Child" or "brain-injured child" as described here, may be, but usually is not mentally defective; may, but usually does not have any motor defects; may be, but usually is not emotionally disturbed, at least during early life. In other words he is to be distinguished from the basically mentally defective, the cerebral palsied and/or the emotionally disturbed, blocked, or frankly psychotic children. Because they represent so small a group compared to other handicapped children, they have received little recognition, and less understanding of their need of highly specialized care, both at home and at school. In bringing out for parents and educators the peculiarities in the behavior of these children, and rational, simple explanations of the psychologic mechanisms involved, the author has indeed performed a much needed service. The chapter on home care is unusually complete for this type of work. The one on education is too superficial to be of much help for professional educators. As is so often true of writings by parents of handicapped children, Lewis, too, tends to describe, explain and prescribe for what is a most bizarre and variegated clinical picture in terms of the relatively restricted experiences and manifestations of his own problem. It should be read by the physician before recommending it to parents since its appropriateness is relatively specific.

TUBERCULOSIS AMONG CHILDREN AND ADULTS, J. Arthur Meyers, M.D., Ph.D., Springfield, Ill., Charles C Thomas, Publisher, 1951, $12.50, 894 pp.

This book is a monumental addition to the literature on the problem of tuberculosis. It is well written in the author's clearcut orderly style. He tells the whole story of tuberculosis, especially in infants and children and young adults. The book is divided in 4 parts: 1. Tuberculosis in Infancy; 2. Tuberculosis in Childhood; 3. Tuberculosis Among Young Adults; 4. Recent Progress in Tuberculosis Control with special articles on the Surgical Treatment of Tuberculosis by Authorities on the Subject.

The subject matter on tuberculosis in infancy and childhood is discussed in a masterful fashion and leaves no part of this important phase unanswered. The author's clinical experience in this field is unlimited and he draws frequently from his deep knowledge of the subject. The section on tuberculous meningitis was written before the advent of streptomycin. The use of this drug has changed the clinical picture of this type of tuberculosis. However the author has discussed the use of this drug extensively in the chapter on drugs. The problem of the primary infection is a classic in itself.

A short but complete chapter has been devoted to bone tuberculosis as seen in children. Many fine illustrations of roentgen film demonstrating these conditions are included here. The first infection type of tuberculosis among young adults is thoroughly discussed and a very fine program is outlined for the solution of this problem.

One chapter on effectiveness of control measures is an outstanding presentation of how the tuberculosis problem should be studied and solved. The use of BCG is discussed pro and con and Dr. Meyers, in no unfailing words, tells how he feels about its use and the reasons for his deductions.

The book is freely illustrated with charts and diagrams and many roentgenograms demonstrating pulmonary conditions. It is a book well recommended to anyone interested in tuberculosis, especially in infants and children. The references are extensive and it is up-to-date with all of the recent advances in the field of phthisiology.

ATTAINING MANHOOD, ed. 2, George W. Corner, M.D., New York, Harper & Brothers, 1952, $1.50, 97 pp.

ATTAINING WOMANHOOD, ed. 2, George W. Corner, M.D., New York, Harper & Brothers, 1952, $1.50, 112 pp.

This is the second edition of a pair of books written to help the adolescent understand sex and human reproduction. This is a difficult task in that one must allow for many differences in background, taste and questions. Dr. Corner has succeeded in giving a readable, complete and systematic exposition of the anatomy and physiology of sexual functioning and reproduction. However, the psychologic reactions and adjustments of the adolescent to the maturation process receive uneven handling by the author. Where the probable anxieties of the reader have been overlooked or where moral issues are raised, the exposition is less satisfactory.

Dr. Corner states that his books are for intelligent boys and girls of high school age and above. He adds that he hopes these books ". . . will help them to understand the biology of human reproduction and its relationship to our lives and problems." He assumes that the elements of human reproduction have already been learned from the parents or from a book written for younger children. "The reason for writing separate books for boys and girls is that there are several phases of the subject of greater interest to one sex than to the other. There are, however, no secrets between the sexes in these matters. . . ." This statement will not overcome the impression created by the fact that there is a separate book for each sex. Indeed the 2 books are so nearly alike that one wonders why the publisher could not have combined them into one book approximately 20 pages longer than either of the present volumes. This book could be titled "Attaining Adulthood" which would be more satisfactory psychologically and economically. At the end of the book there is an excellent reference list of books, pamphlets and educational motion pictures.

The material in the early chapters is presented in an interesting, matter-of-fact manner with numerous examples of sexual maturation in lower animals to provide a perspective. Many of the diagrams are helpful in following the text although the diagram and text explaining the anatomic relations of the gonads and the external genitalia seem unnecessarily difficult to follow for the adolescent reader.

In the chapters dealing with mating, sexual attraction, reproductive cycles and autoerotic activity, Dr. Corner conveys a wholesome attitude to the younger generation by the simplicity and ease with which he describes these matters. The importance of psychologic determinants in human mating are largely neglected. In discussing heterosexual activity the author may arouse a good deal of concern in his reader by the way in which he associates "physical flirtation" with dangers of pregnancy, and leaves little to choose between social contact and "risky intimacies and degrading sexual entanglements." The manner in which the young adults will adapt to the upsurge of sexual strivings raises a broader choice than this. Such a narrow spectrum does not take into account the impact of previous experiences of the individual (in a particular social setting) on his present desires and inhibitions. Venereal diseases are discussed without moralizing and the Kinsey report is briefly summarized in an illuminating fashion. At the end of the books Dr. Corner states, "The book you are reading quite frankly reflects the standards of the high school and college educated people of our own country." It would have been better if the author had stated this as the standards of some of the high school and college educated people of our own country, and had placed these qualifying remarks closer to the beginning of the books. Forewarned in this way the impressionable reader would be more comfortable and better prepared to take advantage of the help these books can give.

These books will be of most interest and help as supplementary reading in a high school or college course in human biology where the student may consult with the instructor about questions and concerns he wants answered as he reads these books, and where a proper background in human biology is assured. These books may also be recommended for young adults who have a relationship with a parent or physician that will facilitate questions or comments to the parental figure that can be discussed in a satisfactory manner. The experience the individual has had as a child with regard to sex curiosity and information will largely determine what use he can make of this information as an adolescent. These books will help, but in the final analysis the presence of a sympathetic and interested adult with whom these matters can be informally discussed is essential.

PSYCHIATRIE SOCIALE DE L'ENFANT (SOCIAL PSYCHIATRY OF THE CHILD), Paris, Le Centre International de l'Enfance, Travaux et Documents II, 1950, 535 pp.

This interesting book, written in French, consists of 535 pages of which 46 are devoted to the description of the many tests now in use in psychologic work, and 33 deal with an extensive "international" bibliography on the subject of child social-psychiatry. The most important part of the book is devoted to the broad subject of child psychiatry itself which is approached through many different angles and by authors of various countries including France, Great Britain, Sweden, Belgium, Spain and Switzerland. This subject was the study theme chosen for the course which the International Child Center in Paris organized from October to December 1950 in Paris and in London and which were sponsored by this Center and the World Health Organization. These lectures had for a main object to bring physicians, students, nurses and social workers from many European countries (especially from those countries which had suffered the most from the war) up to date in the field of child psychiatry. The candidates for these courses were elected by the governments of their own country.

In its 64 chapters, the book summarizes these lectures, and its title, *Child Social Psychiatry* implies that the public health and preventive medicine aspects of the subject have been given consideration. This volume, although in French, will be of special importance to the American reader interested in the opportunity of getting well acquainted with the European points of view on many problems which are connected with child psychiatry. Descriptions of teaching concerning mental hygiene and the problems centering around organization of clinics are also included.

Since infantile experiences have found solid grounds in Freud's psychoanalysis, the pediatrician will find in these pages frequent references to Freud's theories. The reader will notice, however, that many problems have also been approached through different channels other than strict Freudian psychoanalysis.

The psychomotor, intellectual, emotional and social development of the child are studied in detail as are their pathologic disturbances. Other chapters present data on studies of handicapped children, delinquent children, adoption practices, etc., while subjects of a more technical nature such as electroencephalograms and pneumoencephalograms are presented elsewhere in this book. Childhood psychoses are described extensively.

In the last part of the volume, the reader will find some information on the organization of various "Centres" which have been created in France to help the less fortunate children. Similar centers have been established in Great Britain and in other European countries since the last war.

To all pediatricians interested in child psychiatry throughout the world, this book offers an over-all European viewpoint on the subject together with a detailed bibliography. The chapter describing the various tests used in child psychology will be of valuable help, especially to those who have not had the opportunity of getting familiar with their use.

BETTER HOME DISCIPLINE, Norma E. Cutts and Nicholas Moseley, New York, Appleton-Century-Crofts, Inc., 1952, $3.50, 314 pp.

Recognizing that concern about discipline is ever-present in the minds of many parents, the authors of this book made a questionnaire-survey of over 6000 families, and from them culled many vignettes of child behavior which called forth different kinds of discipline.

Excerpts from the replies of parents and children make up a large part of the book; these are accompanied by brief discussions. From them one learns what parents and children today consider worthy of discipline, and the form it takes. While the authors emphasize that there is no one answer that fits every situation, nevertheless one gets the implication from reading their remarks that there is more or less a specific right way of handling each problem. They also tend to relate behavior too specifically to the chronologic age of a child. In this regard there is no scientific evidence for their statement that "parents will probably have to go through four relatively bad periods with each child."

In general, some good general principles of discipline are presented, although frequently the words "punishment" and "discipline" are used interchangeably, as if they meant the same thing. Many child psychologists and other child behavior specialists would not agree with this lack of distinction. Some of the problems of eating are considered too narrowly in terms of discipline and are not related enough to the over-all development of a child. Exception may be made to the recommendation that "sweet-eating is a reason to seek professional advice; it is symptom that something is physically wrong."

Included in the book are some common sense and practical mental health rules for parents which, if followed, would no doubt lead to greater enjoyment of children by their parents. Readers are also told how they might obtain professional help from psychiatrists, psychologists and child guidance clinics.

Lay readers will find this survey interesting, but it is hoped that after reading it they will not lose some of their own spontaneity in dealing with disciplinary problems.

PHYSIOLOGY OF THE NEWBORN INFANT, Clement A. Smith, M.D., ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1951, $7.50.

The second edition of this excellent and already classic monograph is certain to be welcomed by research workers as well as practitioners of pediatrics. It provides a wealth of useful and stimulating information for every physician who takes care of newborn infants, including obstetricians. It is a sign both of the rapid advances in the field and of the author's extensive reading and active participation in pediatric research that only 6 years after the publication of the first edition, almost every chapter has been revised and enriched by new references, and several have been almost completely rewritten. In spite of the coverage and discussion of a large volume of new facts, the size of the book has only increased by about 10 per cent. The author's knowledge and judgment are evident in his restraint in evaluating new data, especially information gained from animal experiments. He repeatedly cautions the reader against overenthusiasm by pointing out, e.g., that nobody knows whether babies benefit from supernormal retention of calcium or weight gain, or substitution of estrogenic stimulation (which normal infants receive during the last few weeks of gestation) to prematures.

As in the first edition, the outstanding feature of the book is the combination of a critical and thoroughly scientific exposition of physiologic observations with very clear, practical suggestions as to the clinical implications of the knowledge gained. A "Clinical Summary" of about two pages at the end of each chapter makes the practical application easily accessible. Another useful feature is a table of normal physiologic, hematologic and chemical values for the newborn period in the back of the book. This table, which contains references to the pages on which each item is discussed and to bibliographic sources, has been revised since the first edition and seems complete and reliable with a few exceptions: The values for serum potassium (taken from a 1927 reference) are much higher than those found in more recent studies and now generally accepted; values for serum creatinine are missing in the table and those given in the text (for cord blood, from a 1931 reference) are about 10 times as high as those observed with more reliable modern methods; and the sedimentation rate is given by the Linzenmeier method which is not commonly used in this country at the present time.

Of the individual chapters, the 2 chapters on respiration are outstanding. They are among those essentially rewritten for this edition. Beside a lucid discussion of physiologic facts gathered from the world literature over more than 50 years, they include many practical points relating to asphyxia and resuscitation at birth (which are still misunderstood and mismanaged in many, even well-reputed, hospitals), interpretation of chest roentgenograms and of clinically observed patterns of breathing. The new edition contains interesting new viewpoints about the (nonchemical) mechanism of onset of respirations at birth, the effect of anesthetics, the difference of pressure required to expand the alveoli for the first few breaths and that for subsequent artificial respiration. Quantitative data are given where most people just think in the form of vague impressions. These quantitative figures constitute important therapeutic considerations, e.g., regarding indications for, and limitations of, drugs, or when applying artificial respiration. As in other chapters, the dynamic and transitory character of physiologic conditions in the fetal and neonatal periods is emphasized.

The chapter on renal physiology also has been thoroughly revised and is excellently written; an amazing amount of information is contained and critically evaluated in 22 short pages. Since the modern literature has been well reviewed and new ideas accepted, one might wish that some of the old charts had also been replaced by newer ones.

The chapters on Nutrition, "Minerals and Vitamins" and Endocrinology are good, down-to-earth, and scientific. Loose thinking and reckless therapeutics are particularly fashionable in these fields; one therefore welcomes the abundant sound advice, e.g., as to managing infants of diabetic, hypo- or hyperthyroid mothers, endocrine therapy of prematures, etc. The author warns against administra-

tion of thiouracil® to pregnant women and against all endocrine therapy (including parathyroid) in newborn infants except, of course, in such frankly pathologic conditions as cretinism or the adrenogenital syndrome. "Postmaturity" is not discussed in this chapter and indeed is only mentioned in one sentence in the book.

The author apologizes for the absence of a chapter on physiology of the central nervous system. The lack of such a chapter is very regrettable since even of the known facts, little is contained in standard texts; and this book in other respects may be considered as such a standard text.

No apologies are needed for including a chapter on neonatal immunology. However, this chapter, with the exception of the very good part about blood groups, is mainly based on older literature and in general is less complete and authoritative than the subjects which are closer to the author's own field of investigation. There is no general discussion of the infant's response to infection, aside from the presence or absence of certain antibodies. In view of the importance of chemotherapeutic and antibiotic therapy in modern practice, one would also welcome a discussion of neonatal bacteriology, e.g., of the normal flora and its rôle in antibiosis and resistance to infections. Aside from a short paragraph on intestinal flora in the chapter on the digestive tract, there are no bacteriologic data in the book.

Every chapter of the book is furnished with an extensive, international, old and new bibliography which contributes to make this book an invaluable source of reference. The subject index at the end of the book is short but surprisingly complete. The clear literary prose, not frequently found in medical publications, enhances the pleasure of reading.